# A STUDY ON CORRELATION OF EJECTION FRACTION AND HBA1C AMONG NON DIABETIC UNSTABLE ANGINA PATIENTS

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# DECLARATION

I , Dr . S.PRAVIN SELVAM solemnly declared that the dissertation titled A STUDY ON CORRELATION OF EJECTION FRACTION AND HBA1C AMONG NON DIABETIC UNSTABLE ANGINA PATIENTS was done by me at Government Stanley Medical College hospital under the guidance and supervision of Prof Dr. P.VASANTHI M.D., Department of Internal Medicine , Stanley Medical College , Chennai.

The dissertation is submitted to the The Tamilnadu Dr.M.G.R.Medical University towards the partial fulfilment of requirement for the award of M.D.Degree ( Branch – 1 ) in General Medicine.

Place : CHENNAI

Date : ( S.PRAVIN SELVAM )

## BONAFIDE CERTIFICATE

This is to certify that A STUDY ON CORRELATION OF EJECTION FRACTION AND HBA1C AMONG NON DIABETIC UNSTABLE ANGINA PATIENTS is a bonafide work performed by S.PRAVIN SELVAM, Post Graduate student in Department of General Medicine , Stanley Medical College , Chennai – 1 under my guidance and supervision in fulfilment of regulations of The Tamilnadu Dr.M.G.R.Medical University for the award of M.D.Degree ( Branch – 1) in General Medicine.

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# A STUDY ON CORRELATION OF EJECTION FRACTION AND HBA1C AMONG NON DIABETIC UNSTABLE ANGINA PATIENTS

## INTRODUCTION

Dr. Huisman and Meyering were the first to isolate Hemoglobin A1c from other different types of Hemoglobin[1] . They used chromatographic column method for isolation of HbA1c in 1958. HbA1c was initially portrayed as a glycoprotein by Bookchin and Gallop in 1968 however its increase in patients with diabetes Mellitus was depicted by Samuel et al in 1969. The use for HbA1c as monitoring tool in the control of blood sugar levels in diabetic patients was proposed in 1976 by Anthony Ceremy .

The nomenclature came from the fact , on the basis of cation exchange chromatography the first separated hemoglobin is HbA . On the order of elution they are further subclassified into HbA1a HbA1b , HbA1c.

The pathogenesis of HbA1c causing damage to the body metabolism is by two distinct process [2].

First is by increasing the highly reactive free radicals which are present in the blood cells .These free radicals also alter the blood cell membranes . These alterations lead to increased blood cell aggregation which further leads to

increased blood viscosity resulting in impaired blood flow through the organs. Second mechanism is by increasing the inflammatory process finally resulting in atherosclerotic plaque, these changes finally Impact the permeability of the inner surface of the endothelium causing leakage.

The production of Pro- inflammatory proteins like Monocyte Adhesion Protein which promotes the aggregation of macrophages in the vessel wall is also elevated leading to atheroma formation.

This glycated hemoglobin pass through the vascular smooth muscle causing inactivation of acetylcholine induced endothelial relaxation by its affinity and bonding to nitric oxide preventing the normal functions of nitric oxide . Ultimately the inactivation of nitric oxide leads to vasoconstriction and increased plague formation. The degradation of blood cells also release heme from them leading to oxidation of endothelial and low density lipoprotein resulting in plague formation .

Though the process of protein synthesis is a common one , the case with hemoglobin is different, as it is a non enzymatic reactions with glucose moiety and the N terminal portion of the beta chain of haemoglobin. This leads to formation of a schiff's base which later on gets converted into 1 - deoxy fructose .This above process is an example of Amadori rearrangement.

# REVIEW OF LITERATURE

In diabetic patients the higher blood glucose levels leads to the attachment of glucose molecules to hemoglobin in the red blood cells[3]. The longer the duration of elevated blood glucose level the higher is the bond between glucose and hemoglobin in the red blood cells .Once the hemoglobin molecule is glycated it cannot be reverted back to the previous free state . The increase in glycated hemoglobin reflects the level and duration of the Rbc's exposure to increased sugar levels. So the assessment of glycated hemoglobin facilitates the effectiveness of therapy and further helps in the monitoring of sugar levels in diabetic patient.

The lifespan of a red blood cell is about 120 days in men and 106 days in women, So the increased level of glycated hemoglobin reflects the increased blood sugar levels of the patients over a period of 120 days.

**Measurement of HbA1c**

A wide variety of methods are used to detect glycated hemoglobin HbA1c.[3]

they include laboratory testing like

- High Performance Liquid Chromatography
- Immuno Assay

- Enzymatic Method
- Coupling Electrophoresis
- Bromide Affinity Chromatography

The mechanism used in devices are

- Immunoassay
- Bromide Affinity Chromatography

INTERPRETATION

The following factors alter the results of HbA1c testing

- Analytical technique
- Age of the subject
- Biological variation

HbA1c values vary between individuals with similar average blood glucose levels as much as 3% [3] .The reliability of HbA1ctesting is questioned in conditions like

- Blood loss - anaemia
- Polycythemia
- After blood transfusion

- Renal diseases
- Liver failure
- Erythropoietin treatment

American Diabetes Association classified [4]patients according to HbA1c as

- Normal - HbA1c less than 5. 6
- Prediabetes / Impaired Fasting Glucose / Impaired Glucose Tolerance - HbA1c between 5.7 to 6.4
- Diabetes mellitus - HbA1c more than or equal to 6.5

Various studies like VKPDS , ACCORD ( action to control cardiovascular risk in diabetes mellitus ) estimated the \ risk of diabetic complications to get reduced by 3% for every 1mmol decrease in HbA1c . They include Diabetic Retinopathy Diabetic Nephropathy, Diabetic Neuropathy and Macrovascular complications .

The target for HbA1c should be individualized by the physicians based on the patient health status and weighed against the impending risk of hypoglycemic episodes. This takes into consideration the patient's ability avert or respond to their own hypoglycemic episodes.

Increased values of HbA1cindicates the long term complications like Coronary Artery Disease, Stroke , Heart failure, Renal failure , Blindness , Neuropathy , Erectile dysfunction and gangrene etc. Improper blood sugar control may lead to impaired wound healing after surgery in many patients and the risk of infection increases in those subset of patients[(2)] .

Lower levels of HbA1c than the expected level is usually found in patients with shortened RBC lifespan like

- Glucose 6 phosphate dehydrogenase deficiency
- Sickle cell disease
- Any disease that affects the red cell life expectancy

In specific conditions like blood transfusion the HbA1c values maybe spuriously low in recipients because the new RBC would have been exposed to high sugar levels only for a short period of time giving false low values under estimating the average blood sugar levels.

Spuriously high HbA1c levels are seen in patients with increase RBC lifespan such as vitamin B12 or Folic acid deficiency

| HbA1c percentage | Average blood glucose levels (mg/dl) | Blood glucose range ( mg/dl) |
|---|---|---|
| 5 % | 97 | 76-120 |
| 6% | 120 | 100-152 |
| 7% | 156 | 120-185 |
| 8% | 183 | 147- 215 |
| 9% | 212 | 170-248 |

INDICATIONS [6]

HbA1c testing is recommended during the confirmation and to monitor the treatment of diabetes . A single result of HbA1c gives a wide variety of information when compared to a fasting blood glucose level report. The advantages of HbA1ctesting over fasting blood glucose levels are

- Patients do not have to fast while testing for HB a1c
- Hba1c gives Information about patient's glycemic status over a period of 3 months

- Better predictor of complications of diabetes mellitus

Frequency for HbA1c testing in Diabetic population [6]

| | |
|---|---|
| Diabetes mellitus type 1 | 3 to 4 times per year |
| Diabetes mellitus type 2 | 2 to 3 times per year |

In pregnancy the diagnosis of diabetes mellitus involves testing for fasting blood sugar levels , postprandial blood sugar levels and glucose tolerance test. There is only very little role for HbA1c testing in pregnancy because of alterations in hematological parameters.

Studies Around The World had also documented that HbA1c has predictive value in assessing the cardiovascular mortality during an acute coronary syndrome however they are not equivocal as they stem from various studies which had different patient selection ideas and different therapy for therapy offered to the patients.

Although many studies in the world have assessed the predictive value of HbA1cin acute coronary syndrome patients among diabetic population[7], only very few studies have assessed the role of HbA1c in predicting the outcome of

acute coronary syndrome among nondiabetic population. However the results of the study vary greatly.

UNSTABLE ANGINA [5]

Definition :-

- New onset (< 2 months ) angina , that is severe and /or frequent ≥3 episodes / day
- Accelerating angina that is those with chronic stable angina who develop angina which is distinctly more frequent, severe , prolonged or precipitated by less exertion than previously
- Angina at rest.

CLASSIFICATION OF UNSTABLE ANGINA [5]

| CLASS | DEFINITION |
|---|---|
| Class I | New onset of severe angina or accelerated angina with no rest pain |
| Class II | Angina at rest within past month but not within preceding 48 hrs ( angina at rest , subacute |
| Class III | Angina at rest within 48 hrs |

| CLINICAL CIRCUMSTANCES | |
|---|---|
| A ( secondary angina ) | Develops in the presence of an extracardiac condition that intensifies MI |
| B ( primary angina ) | Develops in the absence of an extracardiac condition |
| C ( post infarction angina ) | Develops within 2 weeks after acute MI |

Worldwide varieties of theories have been proposed about the pathogenic mechanisms of Unstable Angina. However none of the theories have been able to explain the mechanisms adequately.

Initially many patients with Unstable Angina were found to have atheromatous plagues in their coronary arteries[8]. So a progressive stenosis caused by a large plague was thought to be the reason for ischemic symptoms. However this theory failed due to the fact when assessing the coronary arteries of patients who had chronic stable angina for 2 years and the patient who had Unstable Angina seemed similar . Other patients who had chronic stable angina had larger atheromatous plagues than those with Unstable Angina who presented as initial manifestations of ischemic heart disease.

PLAGUE FISSSURE THEORY [9] :-

The second theory which was better than the above was Plague Fissure Theory . This theory says that the sudden fissuring or rupture of the plague is the main pathogenic mechanism for unstable angina. This fissuring or rupture causes the highly thrombogenic endothelium get exposed to the circulation resulting in the development of platelet rich thrombus. The developed thrombus obstructs the blood flow but do not completely occlude the vessel causing ischemia rather than infarction.

Evidence against Plague Fissure Theory [10] - The First evidence is from clinical observations . We expect the thrombosis at the site of plague rupture to be an acute event . So the patients die or recover from the episode. In both these cases the course of illness short. But in Unstable Angina the symptoms wax and wane over several days or weeks. The mortality is high initially and develops gradually as the time progresses without achieving a steady state. The second evidence is from post mortem changes. The postmortem studies of the patients died due to Unstable Angina did not have evidence of formed atheromatous plagues in the coronary arteries. In addition there was a significant proportion of patients who died due to other causes have evidence of plague fissure with or without thrombosis which makes it a nonspecific finding .

INFLAMMATION THEORY [11] :-

The explanation that inflammation could be the trigger factor in development of Unstable Angina was able to explain both clinical and postmortem observation in patient who died of unstable angina .In short the inflammatory cascade triggered the endothelium leading to thrombosis of the vessel.Support of this theory would be anti inflammatory agents decrease the progression in Unstable Angina. Patients died of Unstable Angina had inflammatory infiltrates in the post mortem examination of coronary arteries. However even patients who died of non cardiac illness also have inflammatory infiltrates in the coronary arteries. From these statements we infer that the progression of patients with Unstable Angina was linked to the severity of inflammatory process. Serum CRP levels can be used as a marker for inflammatory process as they indicate interleukin 6 release which indirectly indicates interleukin 1 release [12]. It is easy to measuren and it has a half life of 19 hours. Serum CRP levels are not increased in patients with variant angina which was caused by spasm however severe they might be. But they are increased in patients with Unstable Angina in whom necrosis has happened. This indicate that CRP levels can be used as a marker in Unstable Angina.

EJECTION FRACTION [5]

It is the fraction of blood ejected from a ventricle of the heart during each systole.

It is calculated by the formula ejection fraction is equal to Stroke Volume / End Diastolic Volume. Normal LVEF is the capacity of the left ventricle to pump the blood during systole into systemic circulation. RVEF is the capacity of the right ventricle to pump the blood during systole into pulmonary circulation. Ejection fraction is best calculated by echocardiography.

Other methods to calculate ejection fraction are [5]

- Computerised Tomography
- Magnetic Resonance Imaging
- Ventriculography
- Single Photon Emission Computerized Tomography
- Radionuclide Angiography
- Muga Scanning

In history the gold standard for measurement of ejection fraction is ventriculography.

In MUGA scanning a radioisotope is injected into the blood and the flow is detected.

Heart Failure is classified on the basis of ejection fraction into Heart Failure With Preserved Ejection Fraction And Heart Failure With Reduced Ejection Fraction.

| | |
|---|---|
| Normal Left Ventricular Ejection Fraction | 66 ± 6 |
| Normal Right Ventricular Ejection Fraction | 67 ± 4.6 |

The blood volumes in the right ventricle equals that of the left ventricle and the ejection fraction of the right ventricle matches with that of the left ventricle under normal physiological conditions . Damages to the muscles of the heart like Myocardial Infarction, Cardiomyopathy ,Atrial Fibrillation decrease ejection fraction of the heart . Ejection fraction has a prognostic value in the evaluation treatment and management of heart failure.

**DIAGNOSIS** [5]

ELECTROCARDIOGRAM [13]

In patients who have Unstable Angina the ECG features suggesting it include inversion of T wave, transient ST segment depression. The occurrence of deviation

in ST segment even if it is only 0.05 millivolt is a very important sign of adverse events in patients who have clinical features classical of unstable angina. The changes in T waves are less specific but they are sensitive for ischemia. The occurrence of deep inversion in T waves greater than 0.3 millivolt and occurrence of new T wave changes which were not present earlier are more significant.

In patients with myocardial infarction there is elevation of ST segment. The elevation in the leads occurs in correspondence to the territory of heart involved. The arterial localisation of obstruction can be made out to an extend from the electrocardiogram. The other changes include formation of q waves and loss of R waves. Most patients who have elevation in the ST segment eventually develop q waves but its magnitude depends on the reperfusion status.

SERUM BIOMARKERS [14]

After an injury to cardiac muscle cell there is leakage of several cardiac proteins into the circulation. The levels at which these cardiac bio markers can be detected depends on molecular weight, local blood, intracellular location of enzymes and lymphatic flow. When the levels of cardiac markers rise to a level such that it exceeds the lymphatic clearance, these biomarkers become detectable in blood.

Cardiac specific troponin T and troponin I are not normally detected in blood but when an attack of injury to cardiac muscle occurs their levels get increased by twenty

folds. Now cardiac troponin I and T are the most preferred biomarkers of injury to cardiac muscle. They are particularly useful when we have doubt of skeletal muscle injury and in very small MI in which the levels of creatine phosphokinase is undetectable. For about seven to ten days after myocardial infarction we can detect the levels of cardiac troponin T and troponin I. Creatine phosphokinase levels are elevated within four to eight hours and in about forty eight to seventy two hours their levels return to normal. The most important disadvantage of using creatine phosphokinase as a cardiac biomarker is that the specificity for cardiac injury is lacking and it will be elevated in conditions causing injury to skeletal muscle including trauma, crush injury, injection, and rhabdomyolysis. This drawback can be reduced by using the isoenzyme of creatine phosphokinase which is CK MB.

ECHOCARDIOGRAPHY

Regional motion wall abnormalities may be present. Echo can be very useful tool for diagnosing coronary artery diseases in which ECG are inconclusive. ECHO can be used to assess the function of the left ventricle post infarction. Right ventricular infarction, aneurysm, thrombus and pericardial effusion can be assessed .Two major complications of myocardial infarction which can be diagnosed using ECHO include acute regurgitation of mitral valve and rupture of the ventricular septum. However in patients with Unstable Angina, the role of echo in dignosis is limited. It provides

certain useful information like ejection fraction, chamber hypertrophy and dilatations.

CORONARY ANGIOGRAPHY

Patients who have Unstable Angina depending upon the TIMI score patient who fall under category two and three must be subjected to angiography and if critical occlusion of arteries is present they must be subjected to intervention.

**INDICATORS OF POOR PROGNOSIS IN UNSTABLE ANGINA PATIENTS [15]**

- Features of congestive cardiac failure during initial period of hospitalisation.
- Premature ventricular beats greater than 10 per hour before discharge
- Reduced left ventricular ejection fraction (<50%)
- Post infarction angina

## MANAGEMENT

The management of unstable angina is similar in Diabetic and non -diabetic subjects

## PRIMARY PREVENTION

The steps taken to prevent the development of risk factors for coronary artery disease constitute primary prevention.

## LIFESTYLE CHANGES DIET AND EXERCISE

The people must be encouraged to take a diet rich in fibres, vegetables, plant sterols and low in saturated fatty acids. The people must be encouraged to exercise. According to the AMERICAN ASSOCIATION OF DIABETES it is recommended that one should exercise for at least thirty minutes per day for five days in week to prevent occurrence of cardiovascular complications. Physical activity need not be exercise as such and might include day to day activities like washing, cleaning, gardening etc…

## WEIGHT REDUCTION

Studies have shown than consuming a diet less in carbohydrate causes reduction in weight drastically only in the initial stages but in order to have continuous

reduction in weight dietary restriction must be combined with increased physical activity .

AVOID SMOKING

Smoking causes release of toxic substances which injures the vascular endothelium and causes vasoconstriction. Hence both active and passive smoking should be avoided.

CONTROL OF DYSLIPIDEMIA [15]

All patients who have a blood LDL level of greater than 70 mg/dl should be started on statins. Patients who have high levels of triglycerides should be started on fibrates.

CONTROL OF HYPERTENSION

JNC 8 guidelines should be followed for control of hypertension. The target level of BP control according to JNC 8 guidelines is 140/90 mm of hg and ace inhibitors are the choice of drugs for control of hypertension.

SPECIFIC THERAPIES

Thrombolytic therapy is contraindicated in Unstable Angina and NSTEMI. Low molecular weight heparin is preferred over unfractionated heparin .In high risk

patients PCI is preferred over conservative treatment and this results in reduction of mortality and morbidity.

ANTI THROMBOTIC AGENTS

It reduces the thrombus and maintains patency of occluded artery. Diabetic patients have increased platelet activation and accelerated turnover of platelets. All the patients of diabetic with CAD need higher doses of aspirin with additional antiplatelet drugs like clopidogrel or ticlopidine.

BETA BLOCKERS

It block the adrenergic stimulation and prevent ventricular remodelling and improve left ventricular function .It reduces the infarct size and decreases the incidence of arrhythmia and improve the survival. Beta blockers also reduce the recurrent ischemia and reinfarction.

ACE INHIBITORS AND ARB

It prevents the ventricular remodelling and subsequent reduction of cardiac failure .it also reduces the recurrent infarction .It delays renal dysfunction .

STATINS

It confers long term protection from cardiovascular events in patients recovering from Unstable angina and also reduces the complications.

## IMPAIRED GLUCOSE TOLERANCE

Impaired glucose tolerance is also called as Pre-diabetes[6] . It is nothing but increase blood sugar levels waving between 110 to 126 mg/dl in fasting and between 140 to 199 after two hours postprandial.It should be confirmed with 75 gram glucose tolerance test at least twice. About 80% of impaired glucose tolerance patient will end up in diabetes mellitus..

Impaired glucose tolerance is a transition state from normal glycemia to frank diabetes.Type 2 Diabetes mellitus and impaired glucose tolerance are a part of metabolic syndrome , Which is also called as syndrome X . This syndrome X include Insulin Resistance, Hypertension , Obesity , Hyperinsulinemia And Dyslipidemia [16] . Impaired glucose tolerance is a major risk factor for diabetes with 20 to 50% of affected patients progressing to diabetes within 10 years. Progression 2 diabetes is not associated with microvascular complications, Nephropathy Retinopathy , Neuropathy.

ETIOLOGY OF GLUCOSE INTOLERANCE [17]

- Obesity is the powerful determinant of glucose intolerance genetic defects of Beta cell function
- Mutation on chromosome 12, Hepatocyte nuclear factor 1, Alpha - MODY3

- Mutation on chromosome 7 p , Glucokinase gene - MODY 1
- Mutation on chromosome 20, HNF 4
- Point mutation in mitochondrial DNA
- Defects in insulin action
- Structure and function of insulin receptors, post receptor signal transduction pathways.
- Type a insulin resistance
- Leprechaunism
- Rabson- Mendelhall syndrome
- Lipoatrophy
- Disease of exocrine pancreas
- Pancreatitis
- Trauma
- Infection
- Pancreatectomy
- Pancreatic cancer
- Cystic fibrosis
- Hemochromatosis
- Fibrocalculous pancreatopathy

Endocrine diseases[18] associated with excess production of insulin antagonist

- Acromegaly
- Cushing syndrome
- Glucagonoma
- Pheochromocytoma
- Hyperthyroidism
- Somatostatinoma
- Aldosteronoma

Drugs or chemical agents [19] with adverse effects on glucose tolerance

- Thiazides
- Glucocorticoids
- calcineurin inhibitors such as cyclosporine and tacrolimus
- Oral contraceptives
- Beta adrenergic agonists
- Nicotinic acid
- Thyroxine
- Pentamidine

- Alpha interferon
- Atypical antipsychotics especially clozapine and olanzapine
- Antiretroviral drugs
- infection associated with beta cell destruction
- Rubella
- Coxsackie virus b
- Mumps
- Cytomegalovirus
- Adenovirus

Genetic syndromes that predisposes an individual to impaired glucose tolerance

- Down syndrome
- Klinefelter syndrome
- Turner syndrome
- Wolfman' syndrome
- Frederick Ataxia

Immune mediated cause of impaired glucose tolerance

- Stiff person syndrome
- Anti insulin receptor abnormalities

Glucose intolerance may be present in many patients with cirrhosis due to decreased hepatic glucose uptake and glycogen synthesis. Other mechanisms include hepatic and peripheral resistance to insulin and serum hormonal abnormality. Glucose intolerance maybe also seen in uremia due to peripheral resistance to the action of insulin.

Actually glucose tolerance will not produce any symptoms or signs but silently it will affect internal organs like heart, kidney, nerves and blood vessels[18] .Impaired glucose tolerance patient are more prone to develop myocardial infarction, systemic hypertension , both macrovascular and microvascular complications[20]

Microvascular complications include [21]

- Retinopathy
- Nephropathy
- Neuropathy

Macrovascular complications include

- Coronary Arterial disease
- Stroke
- Renal papillary necrosis
- lower limb ischemia

## SYMPTOMS AND SIGNS [22]

Normally impaired glucose tolerance patients will not exert any symptoms but fatigue , giddiness, sweating are not specific complaints that are common in Prediabetes. 20 to 30% of Pre diabetic patients have acanthosis nigricans which is a blackish discoloration of neck folds skin , axilla and groin.

## PATHOGENESIS OF IMPAIRED GLUCOSE TOLERANCE

Direct tissue ischemia [23]caused by failure of reactive vasodilation is more important in small vessel complications with inflammatory changes and defects of thrombolysis allow clot formation and potentiate large vessel complications such as myocardial infarction and stroke. Insulin resistance, free fatty acid and inflammatory cytokines released from adipocytes appear more important than hyperglycemia in causing chronic endothelial injury and thrombus formation[24]. This may explain why insulin resistance is associated with complication especially Myocardial Infarction in patients who are still normoglycemic. Direct tissue injury caused by hyperglycemia maybe more important to microvascular complications especially neuropathy.

Insulin resistance and compensatory hyperinsulinemia [25]are linked to metabolic syndrome which is the combination of abdominal obesity, hypertension and

dyslipidemia that is associated with increased vascular disease. Complications are more frequent in insulin resistance patient even before the development of hyperglycemia.

Insulin resistance disrupts insulin regulation of endothelial nitric oxide synthase activity. Insulin resistance was correlated with increased plasma expression of asymmetric Dimethyl Arginine [26] an endogenous nitric oxide synthase inhibitor. Insulin binds with insulin receptor and phosphorylates endothelial nitric oxide synthase. This phosphorylation is lost in insulin resistance. Endothelial proliferation is also a consequence of mitogen signalling associated with insulin resistance. As hyperinsulinemia develops mitogen-activated protein kinase signalling increases , promoting vascular proliferation.

Obesity [27] and insulin resistance promote production of free fatty acids from adipocytes. Excessive free fatty acid induced changes in vasoregulation promote chronic endothelial injury. Free fatty acid inhibit endothelial nitric oxide synthase activation and it helps in generation of reactive oxygen species by increasing peroxidation. Hormones secreted from adipocytes termed Adipo-cytokines [28] plays an important role. Altered secretion of to Adipo-cytokines, Tumor Necrosis Factor Alpha and Adiponectin in obesity and impaired glucose tolerance contributes to endothelial injury and promote early vascular complications. TNF Alpha is a Proinflammatory adipokine that act through sphingolipid second messenger

Ceramide. Ceramide[29] induces oxidative stress and apoptosis in endothelial cells which causes accelerated atherosclerosis .TNF Alpha activation of Ceramide also accelerates insulin resistance by inhibiting insulin receptor coupling to IRS 1. Adiponectin is an adipocyte -derived peptide that inhibits vascular smooth muscle cell proliferation and appears to inhibit macrophage mediated endothelial injury. Adiponectin secretion is reduced in obesity and hyperglycemic states. Increase in type 2 diabetes mellitus is related to life style changes[30] that resulted in overweight, obesity and decreased physical activity levels . These environmental changes superimposed on genetic predisposition increase insulin resistance which in concert with progressive beta cell failure resulting in rising glycemia in non diabetic range[31]. During Pre-diabetic state the risk of cardiovascular disease event is moderately increased with development of diabetes[32] however there is a loss increase in risk of cardiovascular diseases as well as for long term complications affecting eyes Kidneys and Nervous system. The complications of diabetes which are the cause of major morbidity and mortality or related to its duration chronic level of glycemia [33]and other risk factors.

Although both isolated impaired fasting glucose and isolated impaired glucose tolerance are insulin resistance states they differ in their site of insulin resistance[34]. People with isolated impaired fasting glucose predominantly have a partial insulin resistance and normal muscle insulin sensitivity . People with isolated impaired

glucose tolerance have normal to slightly reduced hepatic insulin sensitivity[35] and moderate to severe insulin resistance.

Individuals with both impaired fasting glucose and impaired glucose tolerance manifest both muscle and hepatic insulin resistance[36]. Pattern of insulin secretion also differ between impaired fasting glucose and impaired glucose tolerance. People with isolated impaired fasting glucose have decrease in first phase of insulin secretion ( 0 to 10 min ) after a glucose load. However late phase of insulin secretion ( 60 to 120 minutes) appear normal in patients with isolated fasting glucose. Isolated impaired glucose tolerance also has defect in early phase insulin secretion in response to oral glucose load [37] and in addition has severe deficit in late phase insurance secretion also. Combination of hepatic insulin resistance and defective insulin secretion in isolated impaired fasting glucose results in excessive fasting hepatic glucose production accounting for fasting hyperglycemia. The impairment in early phase insulin response in combination with hepatic insulin resistance result in excessive early rise of plasma glucose in first hour of oral glucose tolerance test. However preservation of late insulin secretion combined with normal muscle insulin sensitivity allows glucose levels to return to preload values in isolated impaired fasting glucose. In contrast in isolated impaired glucose tolerance the defective late insulin secretion combined with muscle and hepatic insulin resistance results in prolonged hyperglycemia after a glucose load. Nowadays fasting plasma glucose

and 2 hour oral glucose tolerance test is preferred to diagnose hyperglycemic States. The prevention of delay in diagnosing glucose intolerance should lead to decrease in duration dependent diabetes related macrovascular and microvascular complications [38]. One of the major reason to recommend therapeutic interventions for individuals with impaired fasting glucose or impaired glucose tolerance is the potential to reduce long to increase risk of cardiovascular diseases associated with diabetes . The strong Association between diabetes and obesity indicate that our first priority is maintenance of healthy weight and obesity prevention [40]. All individuals who are overweight or obese regardless of their blood glucose values should be intensively counseled to lose weight and to exercise regularly. Although several drug successfully reduce the progression 2 diabetes , Metformin was the first drug shown to be very effective. Acarbose appears to be effective as Metformin. But many patients cannot tolerate the gastrointestinal side effects of Acarbose. . Orlistat is similar to Acarbose in effectiveness and is poorly tolerated. It is an over the counter drug. Recently DREAM study indicated that Rosiglitazone was effective in delaying and preventing diabetes but it is costly and it is associated with sevenfold increase of heart failure.

## ORGAN SPECIFIC COMPLICATIONS

EYE Retinopathy - Microvascular aneurysms and rupture leads to non hemorrhagic retinopathy. This is important clue indicating that the patient is progressing into type 2 Diabetes mellitus.

## CARDIOVASCULAR SYSTEM[41]

First system affected in impaired glucose tolerance is cardiovascular system this leads to secondary hypertension associated with half of impaired glucose tolerance cases. Macrovascular thrombi , Atherosclerosis will lead to myocardial infarction. If myocardial infarction is diagnosed in patients with impaired glucose tolerance then it is better to treat the impact glucose tolerance with oral hypoglycemic agents.

## RENAL SYSTEM

Both microvascular and macrovascular thrombi causes Papillary Necrosis and Nephropathy. . Asymptomatic microproteinurea maybe the first clinical clue for diagnosing impaired glucose tolerance in clinical side.

## DIAGNOSIS

### ORAL GLUCOSE TOLERANCE TEST

After 8 to 12 hours of fasting in night 75 gram anhydrous glucose solution has to be taken by the patient over a period of 5 minutes. After 2 hours blood sugar level are

monitored. If the blood sugar level are in between 140 to 199 impaired glucose tolerance is confirmed.

If patient's oral glucose tolerance test, 2 hour postprandial blood sugar level is between 140 to 199 we can confirm it as impaired glucose tolerance. If the patient has a normal fasting sugar and and abnormal oral glucose tolerance test then we have to see HbA1c if the value of HbA1cis around 5.7 to 6.5 then impaired glucose tolerance or Prediabetes is confirmed .All the Diagnostic procedures like oral glucose tolerance test and HbA1c should be repeated twice before committing the final diagnosis of Prediabetes.

TREATMENT OF IMPAIRED FASTING GLUCOSE OR IMPAIRED GLUCOSE TOLERANCE

It involves lifestyle modification with 5 to 10% weight reduction and moderate to intense physical activity for 30 minutes per day or 40 minutes every alternate days.

Individuals with impaired fasting glucose and impaired glucose tolerance and any of the following should undergo Lifestyle modification and / or metformin.

- Age less than 60 years
- Body mass index more than or equal to 35 kg/m2
- Family history of diabetes in first degree relatives
- Elevated triglycerides

- Reduced HDL cholesterol
- Hypertension
- Hba1cmore than or equal to 6

## AIM AND OBJECTIVES

To correlate between Ejection Fraction and HbA1c in Non-Diabetic Unstable Angina patients

## MATERIALS AND METHOD

### PLACE OF STUDY

Emergency & Medical wards

Department of Internal Medicine

Stanley Medical College and Hospital, Chennai

### STUDY POPULATION

First 50 non diabetic patients with unstable angina attending the emergency ward in Government Stanley Hospital are included in this study

### STUDY DESIGN

Cross sectional observational study

## ETHICAL COMMITTEE APPROVAL

Ethical committee approval was obtained for the study

## CASE DEFINITION

- Patients with new onset (< 2 months ) angina , that is severe and /or frequent ≥3 episodes / day
- Patients with accelerating angina that is those with chronic stable angina who develop angina that is distinctly more frequent, severe , prolonged or precipitated by less exertion than previously
- Those with angina at rest.

## INCLUSION CRITERIA

- Non - diabetic patients diagnosed to have unstable angina

## EXCLUSION CRITERIA

- Patients with documented diabetes mellitus
- ST elevation mi (stemi)
- Non-ST elevation mi (nstemi)
- Hba1c ≥ 6.5% or lab tests indicative of diabetes mellitus

- History of definite MI, history of congestive heart failure and history of chronic kidney disease in the past .
- Patients with anemia , pregnancy

METHODOLOGY

First 50 Non diabetic Unstable Angina patients admitted to emergency & medical wards at Stanley medical college hospital Chennai are included in the present study. Informed consent was obtained from the subjects. Detailed medical history will be collected from each patient. Patients were subjected for clinical examination followed by relevant investigations.

The patients undergo the following investigations.

- Hba1c testing by enzymatic method.
- Ecg
- Trans thoracic Echo is done in each patient and 3-4 cardiac cycles were analysed to get best phase for better outcome of results. Ef is calculated by Simpsons method

The first 50 Non diabetic unstable angina patients , admitted in emergency wards were subjected to a trans thoracic echocardiography.

On the basis of ejection fraction they are classified into

- Ejection fraction less than 50 group
- Ejection fraction more than or equal to 50 group

Serum samples for HbA1c testing will be obtained from each patient after echocardiography. HbA1c testing will be done by enzymatic method . Then correlation of ejection fraction and HbA1c will be analysed statistically.

## STUDY PERIOD

The study period is from march 2017 to September 2017

## HUMAN SUBJECT PROTECTION

The full protocol along with draft questionnaire and Informed consent will be kept in Institutional ethical Committee and approval will be obtained.

## INFORMED CONSENT

Consent form will be written in both English and Tamil and consent will be obtained from the participant, confidentiality will be maintained.

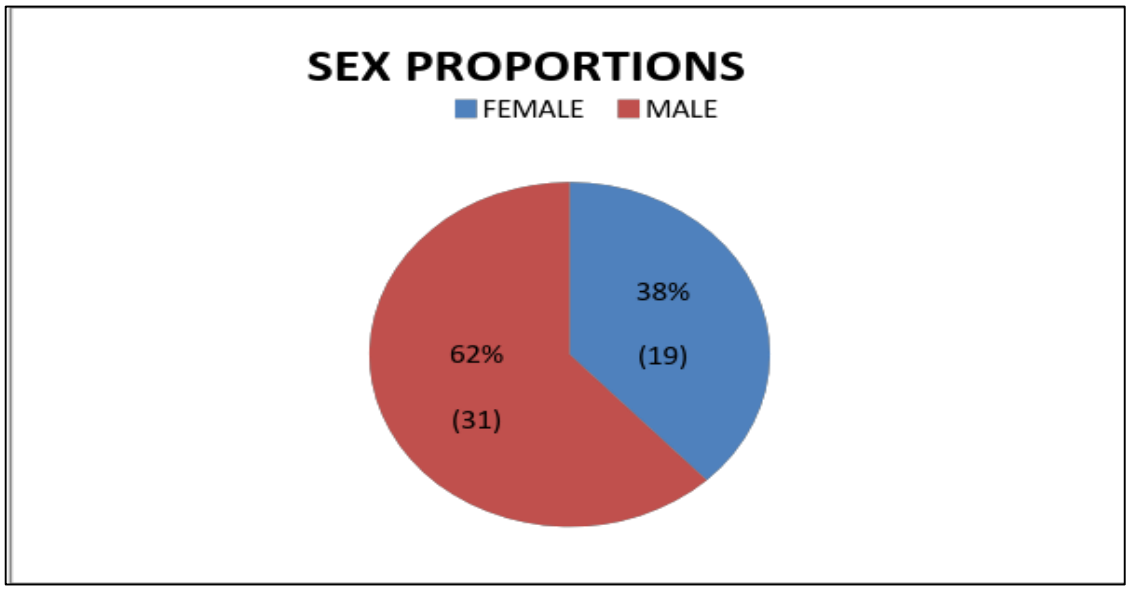
# RESULTS AND DISCUSSION

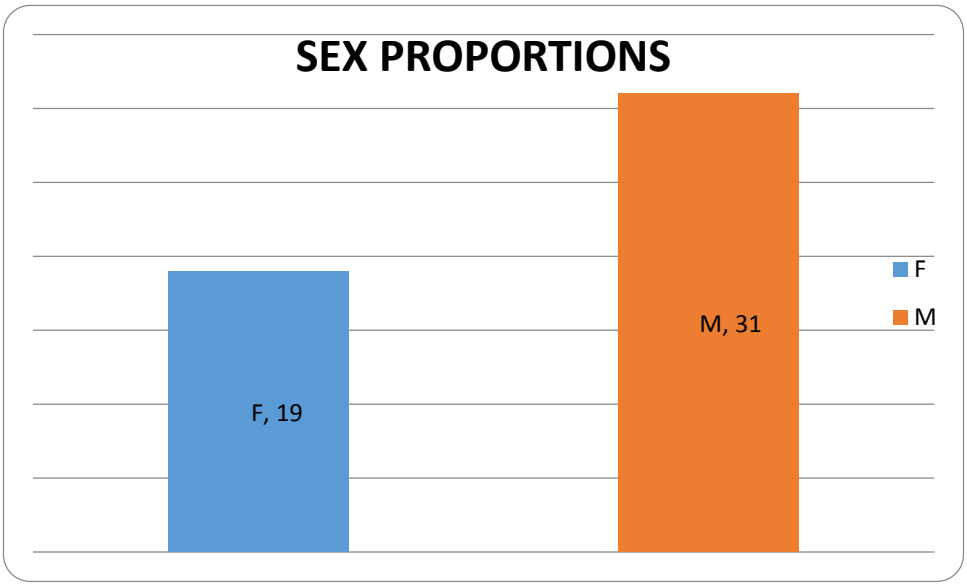
Descriptive statistics was done for all data and were reported in terms of mean values and percentages. Suitable statistical tests of comparison were done. Continuous variables were analysed with the unpaired t test.. Categorical variables were analysed with the Chi-Square Test and Fisher Exact Test. Statistical significance was taken as $P < 0.05$. The data was analysed using Epi info 7 and Microsoft Excel 2007.

STATISTICAL ANALYSIS

POPULATION

| | | Frequency | Percent |
|---|---|---|---|
| Valid | F | 19 | 38.0 |
| | M | 31 | 62.0 |
| | Total | 50 | 100.0 |






The total population subjected to study is 50

Among the 50 subjects Males were 31 and Females were 19.

Males contribute 62% to  the study population

Females contribute 38 % to  the study population.

## AGE STATISTICS

| Frequency | Percent | Cum % | Age | Percent | Cum % |
|---|---|---|---|---|---|
| 39 | 1 | 2.0 | 56 | 4 | 8.0 |
| 40 | 5 | 10.0 | 57 | 1 | 2.0 |
| 42 | 2 | 4.0 | 58 | 3 | 6.0 |
| 44 | 1 | 2.0 | 59 | 1 | 2.0 |
| 45 | 1 | 2.0 | 60 | 1 | 2.0 |
| 47 | 4 | 8.0 | 62 | 3 | 6.0 |
| 48 | 1 | 2.0 | 63 | 2 | 4.0 |
| 49 | 1 | 2.0 | 64 | 1 | 2.0 |
| 50 | 1 | 2.0 | 65 | 1 | 2.0 |
| 51 | 2 | 4.0 | 66 | 3 | 6.0 |
| 54 | 1 | 2.0 | 67 | 1 | 2.0 |
| 55 | 3 | 6.0 | 68 | 2 | 4.0 |
| | | | 70 | 4 | |
| | | | Total | 50 | |

## MEAN AGE OF THE POPULATION

| | Obs | Total | **Mean** | Variance | Std Dev |
|---|---|---|---|---|---|

| | | | | | |
|---|---|---|---|---|---|
| | 50.0000 | 2764.0000 | **55.2800** | 94.1241 | 9.7018 |

| | Minimum | 25% | Median | 75% | Maximum | Mode |
|---|---|---|---|---|---|---|
| | 39.0000 | 47.0000 | 56.0000 | 63.0000 | 70.0000 | 40.0000 |

**MEAN AGE STRATAVAR = SEX**

**FEMALES**

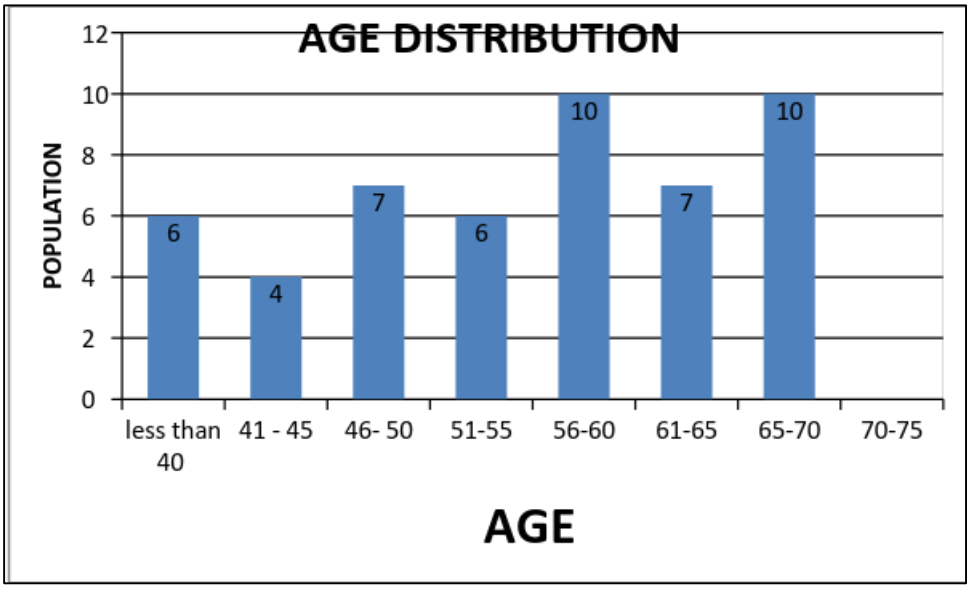
| | Obs | Total | **Mean** | Variance | Std Dev |
|---|---|---|---|---|---|
| | 19.0000 | 1086.0000 | **57.1579** | 96.1404 | 9.8051 |

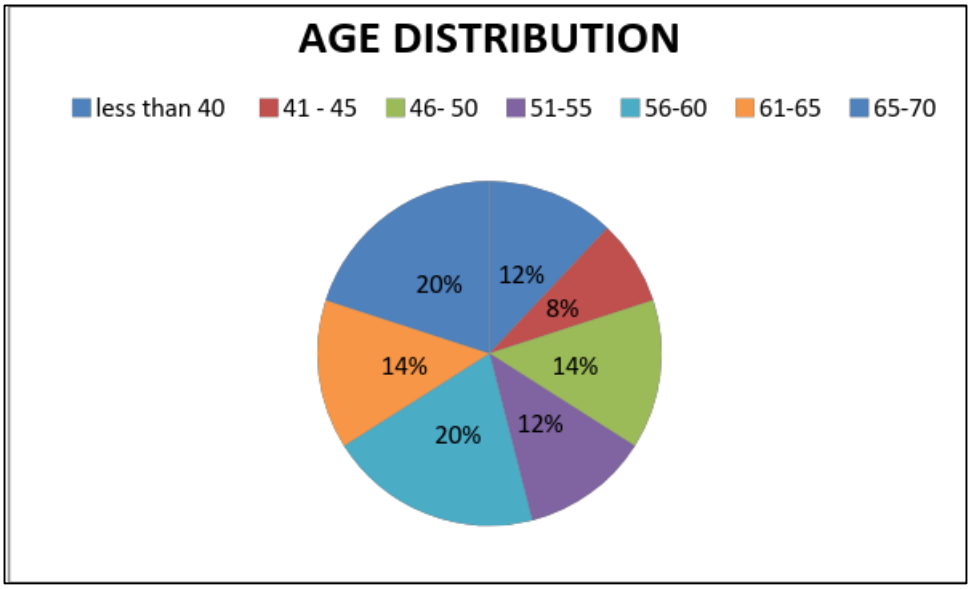
| | Minimum | 25% | Median | 75% | Maximum | Mode |
|---|---|---|---|---|---|---|
| | 40.0000 | 47.0000 | 58.0000 | 66.0000 | 70.0000 | 47.0000 |

**MALES**

| | Obs | Total | **Mean** | Variance | Std Dev |
|---|---|---|---|---|---|
| | 31.0000 | 1678.0000 | **54.1290** | 92.4495 | 9.6151 |

| | Minimum | 25% | Median | 75% | Maximum | Mode |
|---|---|---|---|---|---|---|
| | 39.0000 | 47.0000 | 56.0000 | 62.0000 | 70.0000 | 40.0000 |






Mean age of the population is 55 ( 55.2800 )

Mean age stratified sex wise

| | |
|---|---|
| Male | 54.1290 |
| Female | 57.1579 |

The mean age of females is 54 ( 54.1290)

The mean age of males is 57.15 (57.1579)

Age groups 55-60 and 65 -70 have highest population frequency .

**EJECTION FRACTION**

| EF | Frequency | Percent |
|---|---|---|
| **40** | 5 | 10.00% |
| **42** | 1 | 2.00% |
| **45** | **12** | **24.00%** |
| **46** | 1 | 2.00% |
| **48** | 10 | 20.00% |
| **52** | 3 | 6.00% |
| **55** | 3 | 6.00% |
| **60** | 4 | 8.00% |
| **62** | 1 | 2.00% |
| **63** | 1 | 2.00% |
| **64** | 1 | 2.00% |
| **65** | 3 | 6.00% |
| **66** | 1 | 2.00% |
| **68** | 4 | 8.00% |
| **Total** | 50 | 100.00% |

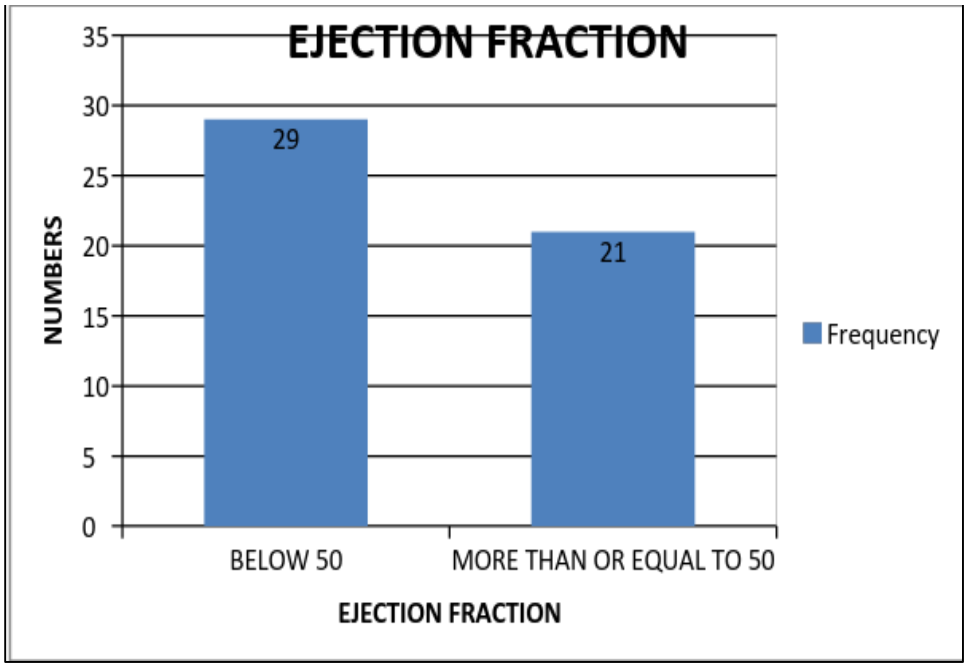
Ejection fraction value of 45 % had the maximum frequency of 12 subjects . which contribute to 24 % of the entire population .

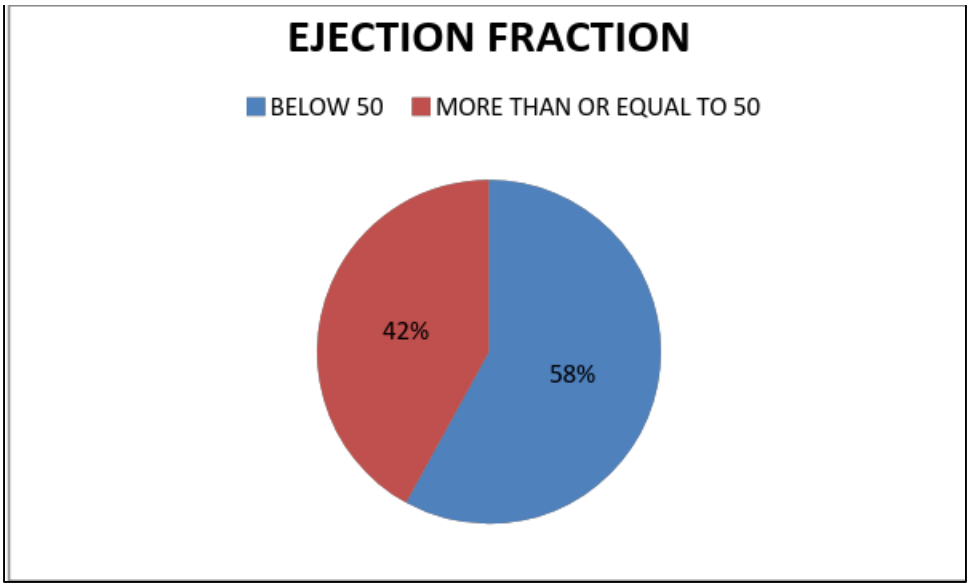
Ejection fraction values of 42% , 46 % , 62-64%, 66 %had the least frequency of 1 subject . which contribute to 2b % of the entire population

| EF | Frequency | Percent |
|---|---|---|
| BELOW 50 | 29 | 58.00% |
| **MORE THAN OR EQUAL TO 50** | 21 | 42.00% |
| **Total** | 50 | 100.00% |

58 percent ( 29 ) of the population have EF less than 50 %

42 percent ( 21 ) of the population have EF more than 50 %






In the study population patients with ejection fraction more than or equal to 50 are lower in frequency when compared to patients with ejection fraction  less than 50.

**MEAN  EF OF STUDY POPULATION**

| | Obs | Total | **Mean** | Variance | Std Dev |
|---|---|---|---|---|---|
| | 50.0000 | 2591.0000 | **51.8200** | 81.1710 | 9.0095 |

| | Minimum | 25% | Median | 75% | Maximum | Mode |
|---|---|---|---|---|---|---|
| | 40.0000 | 45.0000 | 48.0000 | 60.0000 | 68.0000 | 45.0000 |

**MEAN EF STRATAVAR =SEX**

**FEMALES**

| | Obs | Total | **Mean** | Variance | Std Dev |
|---|---|---|---|---|---|
| | 19.0000 | 941.0000 | **49.5263** | 70.2632 | 8.3823 |

| | Minimum | 25% | Median | 75% | Maximum | Mode |
|---|---|---|---|---|---|---|
| | 40.0000 | 45.0000 | 48.0000 | 55.0000 | 68.0000 | 45.0000 |

**MALES**

| | Obs | Total | **Mean** | Variance | Std Dev |
|---|---|---|---|---|---|
| | 31.0000 | 1650.0000 | **53.2258** | 85.0473 | 9.2221 |

| | Minimum | 25% | Median | 75% | Maximum | Mode |
|---|---|---|---|---|---|---|
| | 40.0000 | 45.0000 | 48.0000 | 62.0000 | 68.0000 | 45.0000 |

The mean EF of the population is  52 ( 51.82 )

The mean EF  of Males is  53 (53. 22)

The mean EF of  Females is  49.5 ( 49.52 )

**HbA1c STATISTICS**

| HBA1C | Frequency | Percent |
|---|---|---|
| **4.9** | 1 | 2.00% |
| **5.1** | 1 | 2.00% |
| **5.2** | 1 | 2.00% |
| **5.3** | 4 | 8.00% |
| **5.4** | 1 | 2.00% |
| **5.5** | 4 | 8.00% |
| **5.6** | 4 | 8.00% |
| **5.7** | 1 | 2.00% |
| **5.8** | 1 | 2.00% |
| **5.9** | 4 | 8.00% |
| **6** | 1 | 2.00% |
| **6.1** | **9** | **18.00%** |
| **6.2** | 7 | 14.00% |
| **6.3** | 5 | 10.00% |
| **6.4** | 6 | 12.00% |
| **Total** | 50 | 100.00% |

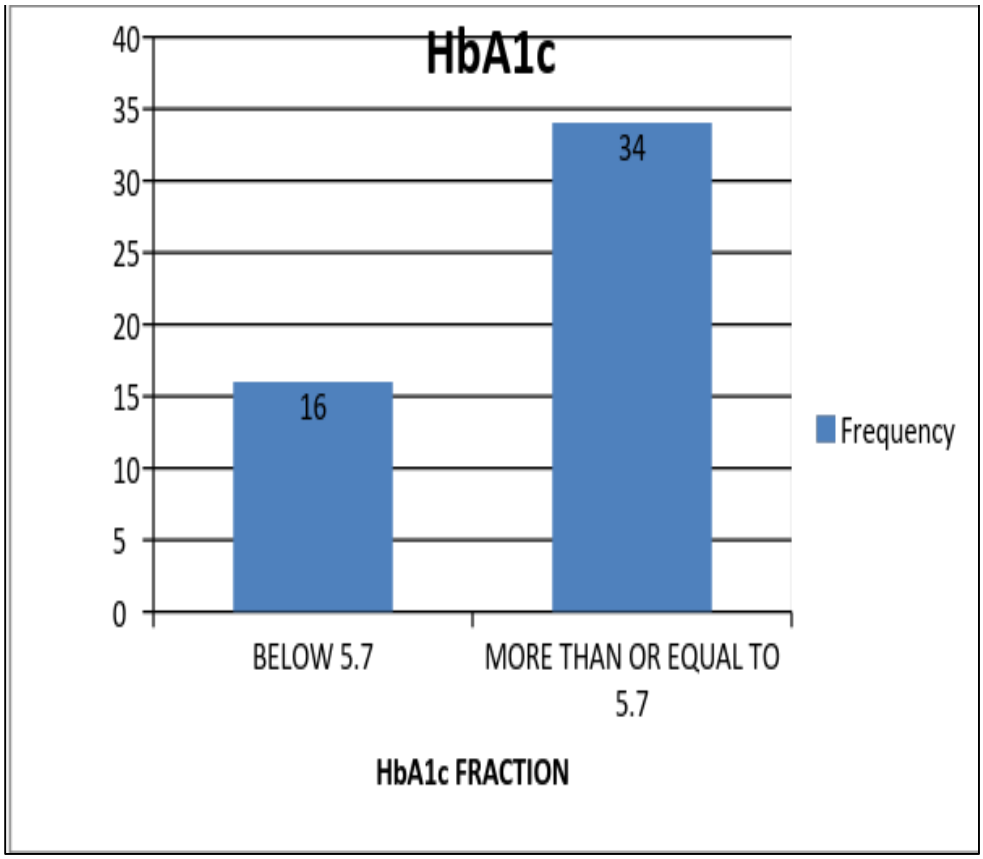
In the study population HbA1c value of 6.1 had the maximum frequency of 9 subjects . this contributes to 18 % of the total population.

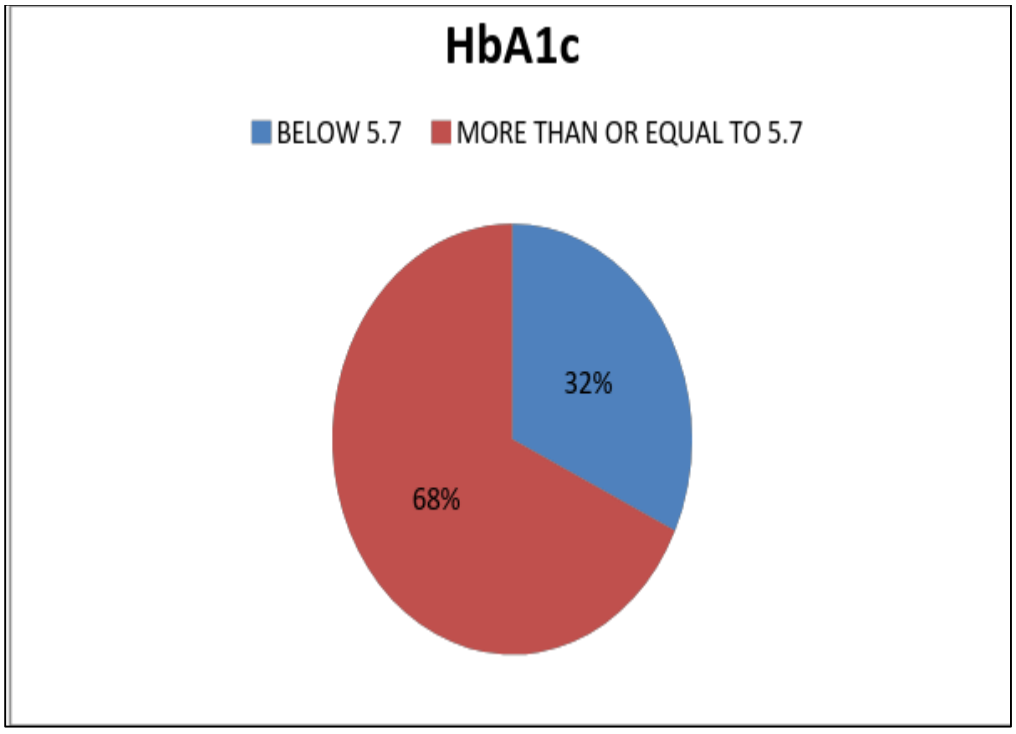
In the study population HbA1c value of 6.2 had the second highest frequency of 7 subjects . this contributes to 14 % of the total population.

| HBA1C | Frequency | Percent |
|---|---|---|
| **BELOW 5.7** | 16 | 32.00% |
| **ABOVE OR EQUAL TO 5.7** | 34 | 68.00% |
| **Total** | 50 | 100.00% |

32 percent of population have HbA1c less than 5.7 with a frequency of 16 subjects

68 percent of population have HbA1c equal to or more than 5.7 with a frequency of 34 subjects.


HbA1c
40
35
30
25
20
15
10
5
0
34
16
Frequency
BELOW 5.7
MORE THAN OR EQUAL TO 5.7
HbA1c FRACTION


HbA1c
BELOW 5.7
MORE THAN OR EQUAL TO 5.7
32%
68%

In the study population patients with HbA1c more than or equal to 5.7 have two fold high frequency when compared to patients with HbA1c less than 5.7 .

**MEAN HbA1c OF THE POPULATION**

| | Obs | Total | **Mean** | Variance | Std Dev |
|---|---|---|---|---|---|
| | 50.0000 | 295.5000 | **5.9100** | 0.1666 | 0.4082 |

| | Minimum | 25% | Median | 75% | Maximum | Mode |
|---|---|---|---|---|---|---|
| | 4.9000 | 5.6000 | 6.1000 | 6.2000 | 6.4000 | 6.1000 |

**MEANS HbA1c STRATAVAR = SEX**

**FEMALES**

| | Obs | Total | **Mean** | Variance | Std Dev |
|---|---|---|---|---|---|
| | 19.0000 | 114.5000 | **6.0263** | 0.1332 | 0.3649 |

| | Minimum | 25% | Median | 75% | Maximum | Mode |
|---|---|---|---|---|---|---|
| | 5.2000 | 5.8000 | 6.1000 | 6.3000 | 6.4000 | 6.4000 |

**MALES**

| | Obs | Total | **Mean** | Variance | Std Dev |
|---|---|---|---|---|---|
| | 31.0000 | 181.0000 | **5.8387** | 0.1785 | 0.4224 |

| | Minimum | 25% | Median | 75% | Maximum | Mode |
|---|---|---|---|---|---|---|
| | 4.9000 | 5.5000 | 6.0000 | 6.2000 | 6.4000 | 6.1000 |

The mean HbA1c of the population is 5.9 (5.91)

The mean HbA1c among Males is 5.9 ( 5.8387)

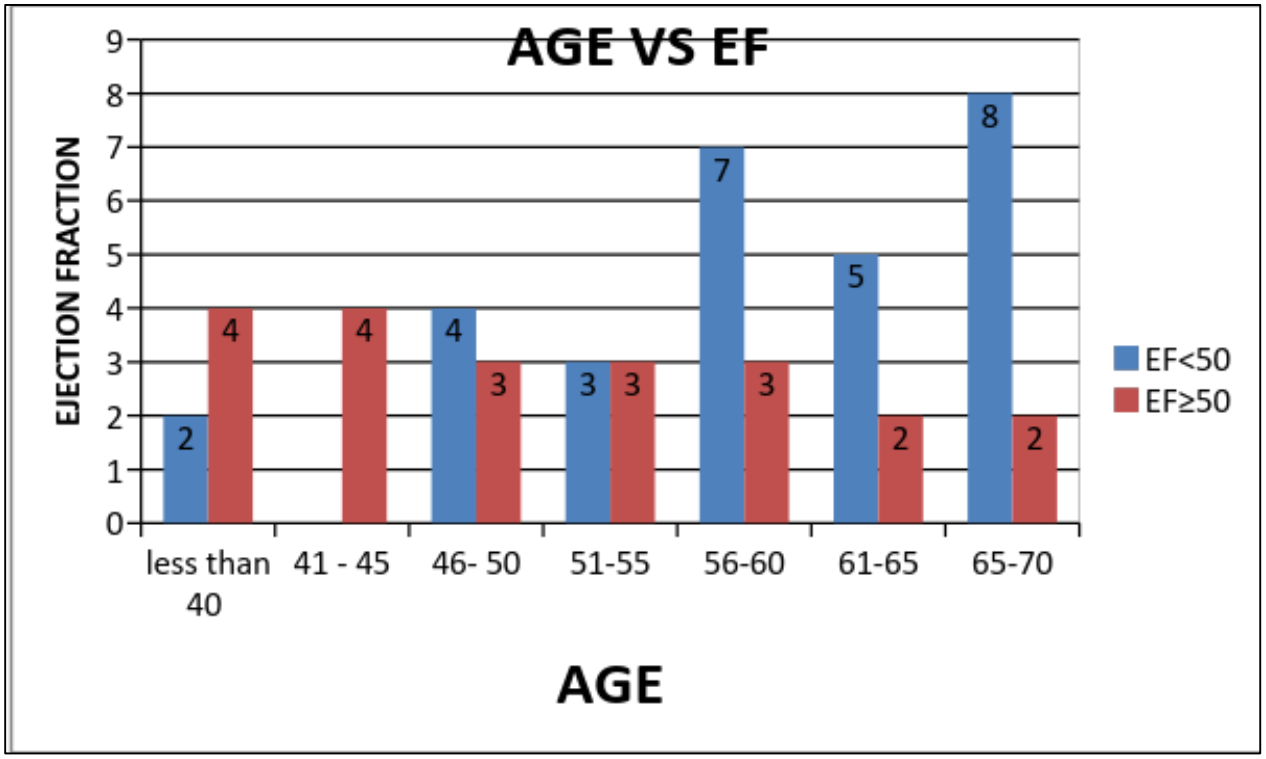
The mean HbA1c among Females is 6.0 ( 6.026)

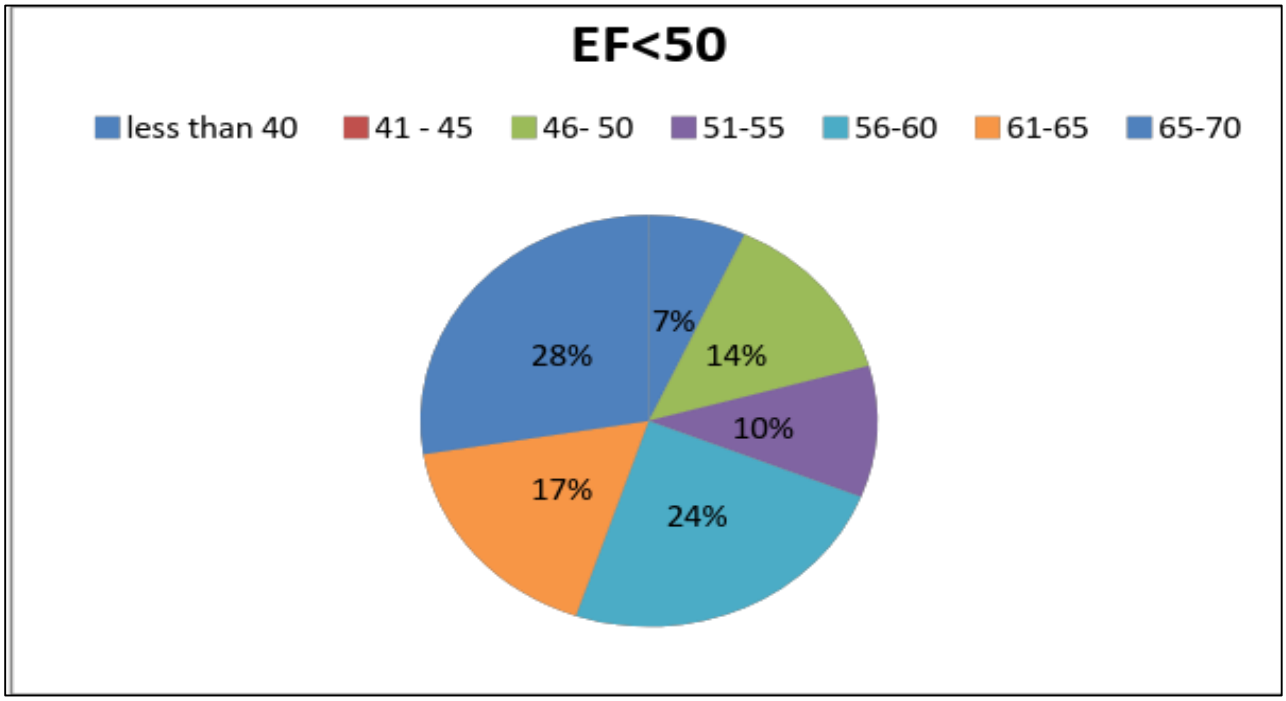
## AGE AND EJECTION FRACTION

| | EJECTION FRACTION | | | | EJECTION FRACTION | | |
|---|---|---|---|---|---|---|---|
| **AGE** | **BELOW 50** | **MORE THAN OR EQUAL TO 50** | **Total** | **AGE** | **BELOW 50** | **MORE THAN OR EQUAL TO 50** | **TOTAL** |
| **39** | 0 | 1 | 1 | **56** | 4 | 0 | 4 |
| **40** | 2 | 3 | 5 | **57** | 0 | 1 | 1 |
| **42** | 0 | 2 | 2 | **58** | 1 | 2 | 3 |
| **44** | 0 | 1 | 1 | **59** | 1 | 0 | 1 |
| **45** | 0 | 1 | 1 | **60** | 1 | 0 | 1 |
| **47** | 3 | 1 | 4 | **62** | 2 | 1 | 3 |
| **48** | 1 | 0 | 1 | **63** | 1 | 1 | 2 |
| **49** | 0 | 1 | 1 | **64** | 1 | 0 | 1 |
| **50** | 0 | 1 | 1 | **65** | 1 | 0 | 1 |
| **51** | 2 | 0 | 2 | **66** | 2 | 1 | 3 |
| **54** | 1 | 0 | 1 | **67** | 1 | 0 | 1 |
| **55** | 0 | 3 | 3 | **68** | 1 | 1 | 2 |
| | | | | **70** | 4 | 0 | 4 |
| | | | | | 29 | 21 | 50 |

Age group 65-70 had the highest frequency of patients with EF less than 50

Age group less than 40 & 41- 45 had the highest frequency of patients with EF more than or equal to 50

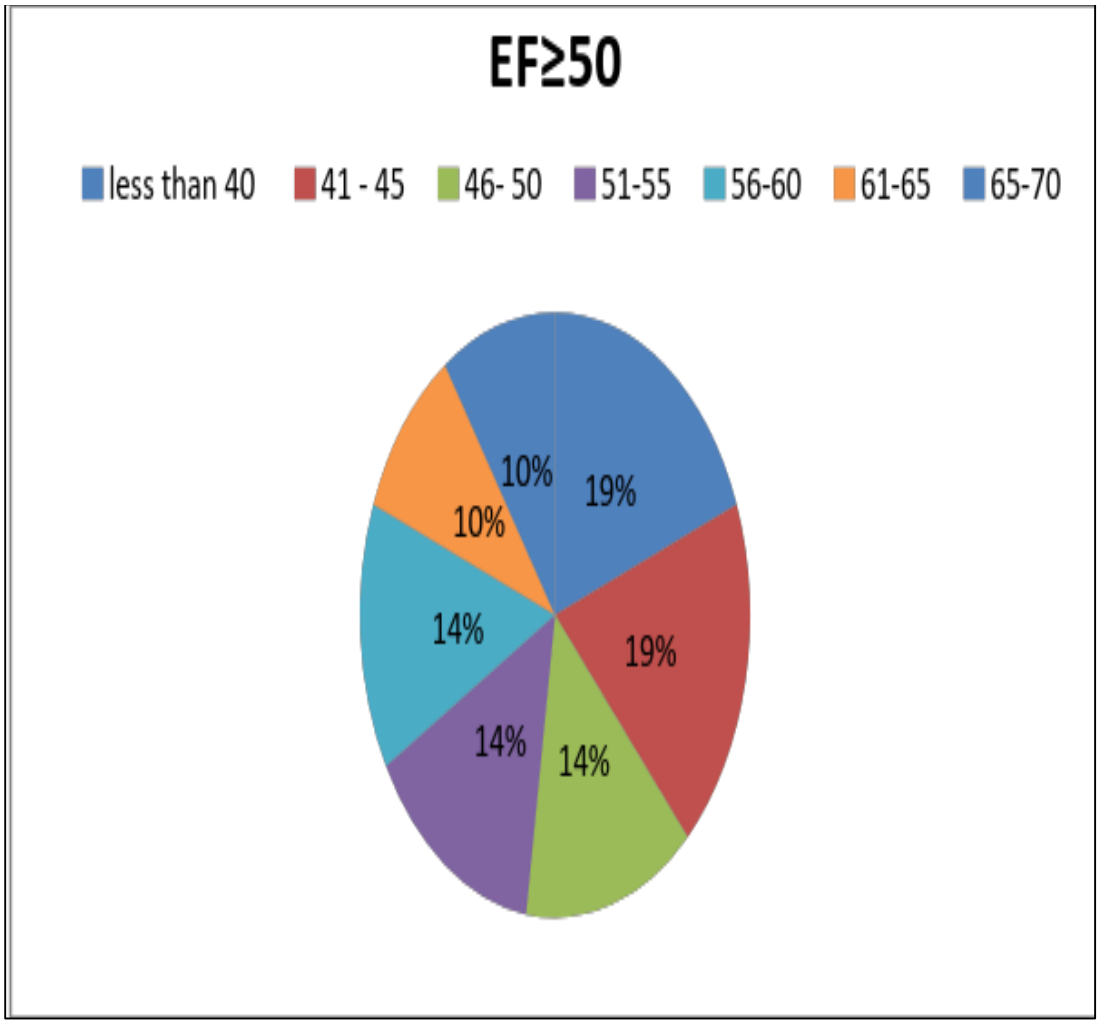

AGE VS EF
EJECTION FRACTION
9
8
7
6
5
4
3
2
1
0
2
4
4
4
3
3
3
7
3
5
2
8
2
less than 40
41 - 45
46- 50
51-55
56-60
61-65
65-70
AGE
EF<50
EF≥50


EF<50
less than 40
41 - 45
46- 50
51-55
56-60
61-65
65-70
7%
14%
10%
24%
17%
28%

In EF less than 50 group maximum frequency of population is in age group 65-70

EF less than 50 group least  frequency of population is in age group 41-45 .

In EF ≥ 50 group maximum frequency of population is in age groups less than 40 & 41-45  and the least frequency is in age group 61-65 years.



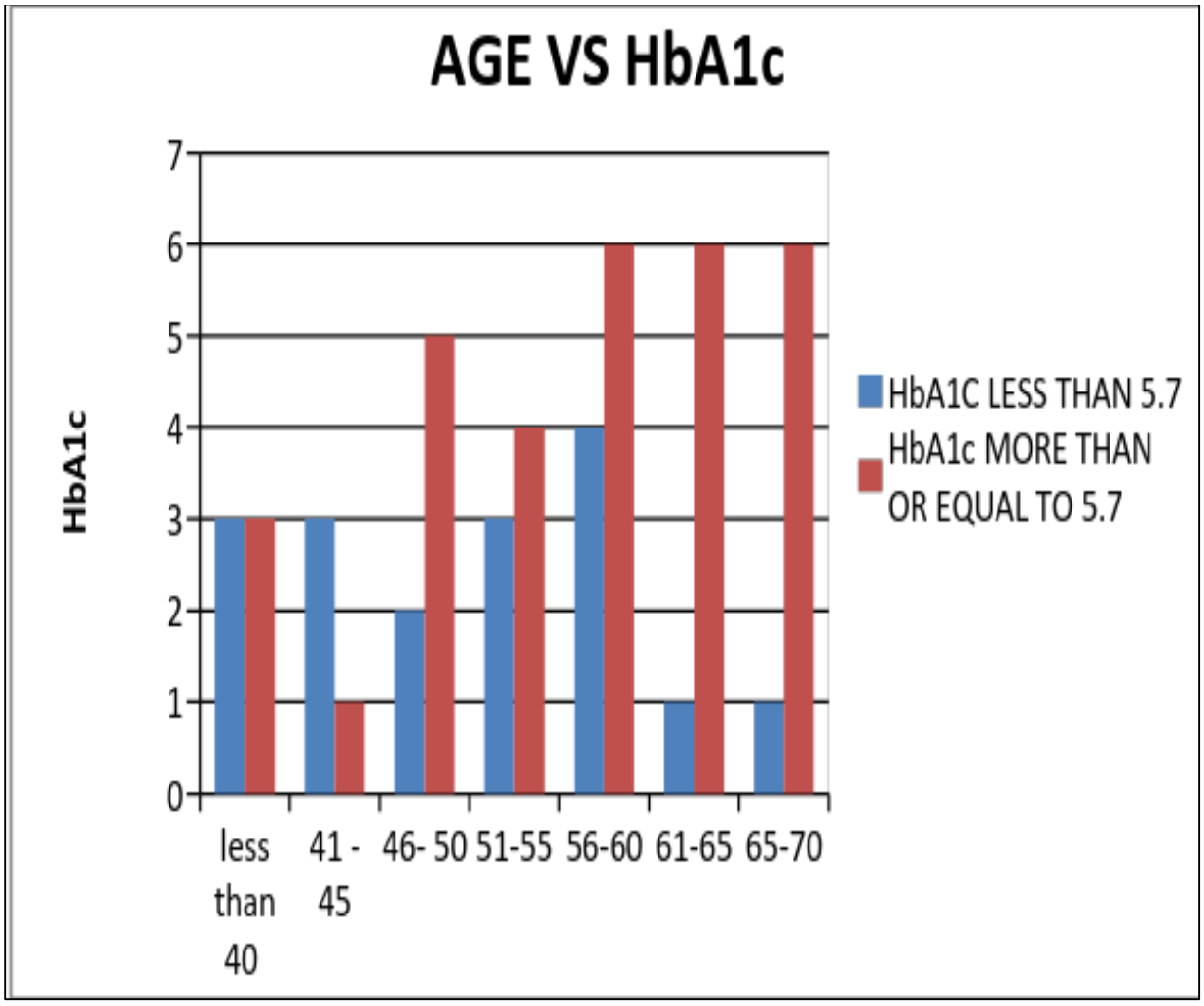
The assessment of age group less than 40 years, patients with EF≥50 years have two fold increased frequency when compare to patients with EF <50 .

The assessment of age group 65-70 years, patients with EF<50 years have four fold increased frequency when compare to patients with EF ≥50 .

## AGE AND HbA1c CROSS TABULATION

| | HbA1c | | | | HbA1c | | |
|---|---|---|---|---|---|---|---|
| **AGE** | **LESS THAN 5.7** | **MORE THAN OR EQUAL TO 5.7** | **Total** | **Age** | **LESS THAN 5.7** | **MORE THAN OR EQUAL TO 5.7** | **Total** |
| **39** | 1 | 0 | 1 | **57** | 1 | 0 | 1 |
| **40** | 2 | 3 | 5 | **58** | 2 | 1 | 3 |
| **42** | 2 | 0 | 2 | **59** | 0 | 1 | 1 |
| **44** | 1 | 0 | 1 | **60** | 0 | 1 | 1 |
| **45** | 0 | 1 | 1 | **62** | 0 | 3 | 3 |
| **47** | 1 | 3 | 4 | **63** | 1 | 1 | 2 |
| **48** | 0 | 1 | 1 | **64** | 0 | 1 | 1 |
| **49** | 0 | 1 | 1 | **65** | 0 | 1 | 1 |
| **50** | 1 | 0 | 1 | **66** | 0 | 3 | 3 |
| **51** | 0 | 2 | 2 | **67** | 0 | 1 | 1 |
| **54** | 0 | 1 | 1 | **68** | 1 | 1 | 2 |
| **55** | 2 | 1 | 3 | **70** | 0 | 4 | 4 |
| **56** | 1 | 3 | 4 | **TOTAL** | 16 | 34 | 50 |

In the study population patients with HbA1c more than or equal to 5.7 have two fold increased frequency when compared to patients with HbA1c less than 5.7




In patients with HbA1c less than 5.7 the maximum frequency of population was in age group 56-60 . In patients with HbA1c less than 5.7 the least frequency of population was in age group 61-65 & 65 – 70.

In patients with HbA1c more than or equal to 5.7 the maximum frequency of population was in age groups 56-60 & 61-70 . In patients with HbA1c more than or equal to 5.7 the least  frequency of population was in age groups 41-45.

**AGE AND SEX**

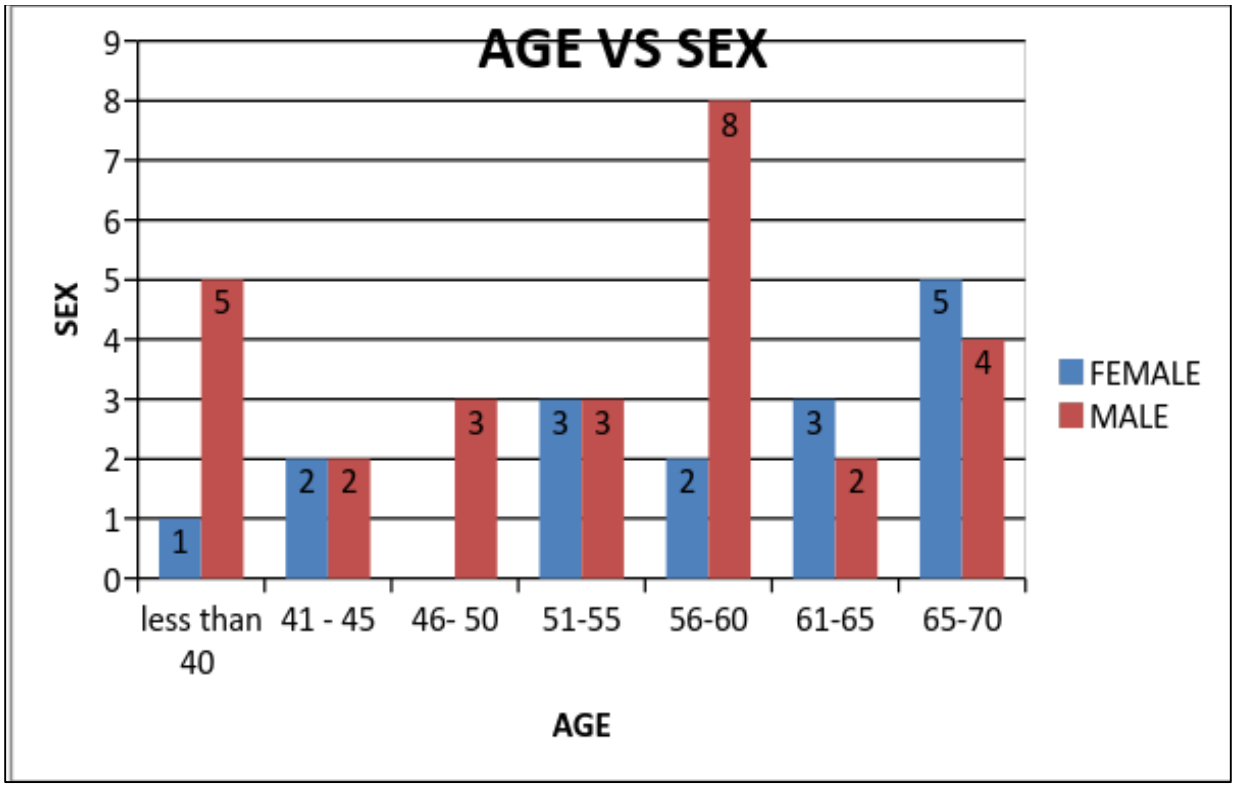
| | SEX | | | | SEX | | |
|---|---|---|---|---|---|---|---|
| **AGE** | **FEMALE** | **MALE** | **Total** | **AGE** | **FEMALE** | **MALE** | **Total** |
| **39** | 0 | 1 | 1 | **57** | 0 | 1 | 1 |
| **40** | 1 | 4 | 5 | **58** | 1 | 2 | 3 |
| **42** | 1 | 1 | 2 | **59** | 0 | 1 | 1 |
| **44** | 0 | 1 | 1 | **60** | 0 | 1 | 1 |
| **45** | 1 | 0 | 1 | **62** | 1 | 2 | 3 |
| **48** | 0 | 1 | 1 | **64** | 1 | 0 | 1 |
| **49** | 0 | 1 | 1 | **65** | 1 | 0 | 1 |
| **50** | 0 | 1 | 1 | **66** | 2 | 1 | 3 |
| **51** | 2 | 0 | 2 | **67** | 0 | 1 | 1 |
| **54** | 0 | 1 | 1 | **68** | 1 | 1 | 2 |
| **55** | 1 | 2 | 3 | **70** | 2 | 2 | 4 |
| **56** | 1 | 3 | 4 | **TOTAL** | 19 | 31 | 50 |

The maximum frequency of Males are in age group 56-60 .

The least frequency of Males are in age group 41-45 & 61-65.

The maximum frequency of Females are in age group 65-70

The least frequency of Females are in age group less than 40 .




When assessing the age group less than 40 years males had five fold increased frequency when compare to females

When assessing the age group 65- 70 years females and male have similar frequency.

Significant difference in sex ratio is also seen in age group 56- 60 years

## HbA1c AND SEX

| | | | |
|---|---|---|---|
| **HBA1C** | **FEMALE** | **MALE** | **Total** |
| **4.9** | 0 | 1 | 1 |
| **5.1** | 0 | 1 | 1 |
| **5.2** | 1 | 0 | 1 |
| **5.3** | 1 | 3 | 4 |
| **5.4** | 0 | 1 | 1 |
| **5.5** | 0 | 4 | 4 |
| **5.6** | 1 | 3 | 4 |
| 5.7 | 1 | 0 | 1 |
| **5.8** | 1 | 0 | 1 |
| **6** | 0 | 1 | 1 |
| **6.1** | 3 | 6 | 9 |
| **6.2** | 3 | 4 | 7 |
| **6.3** | 2 | 3 | 5 |
| **6.4** | 4 | 2 | 6 |
| **TOTAL** | 19 | 31 | 50 |

In this study HbA1c values 6.1 and 6.2 had the highest frequency of Females and

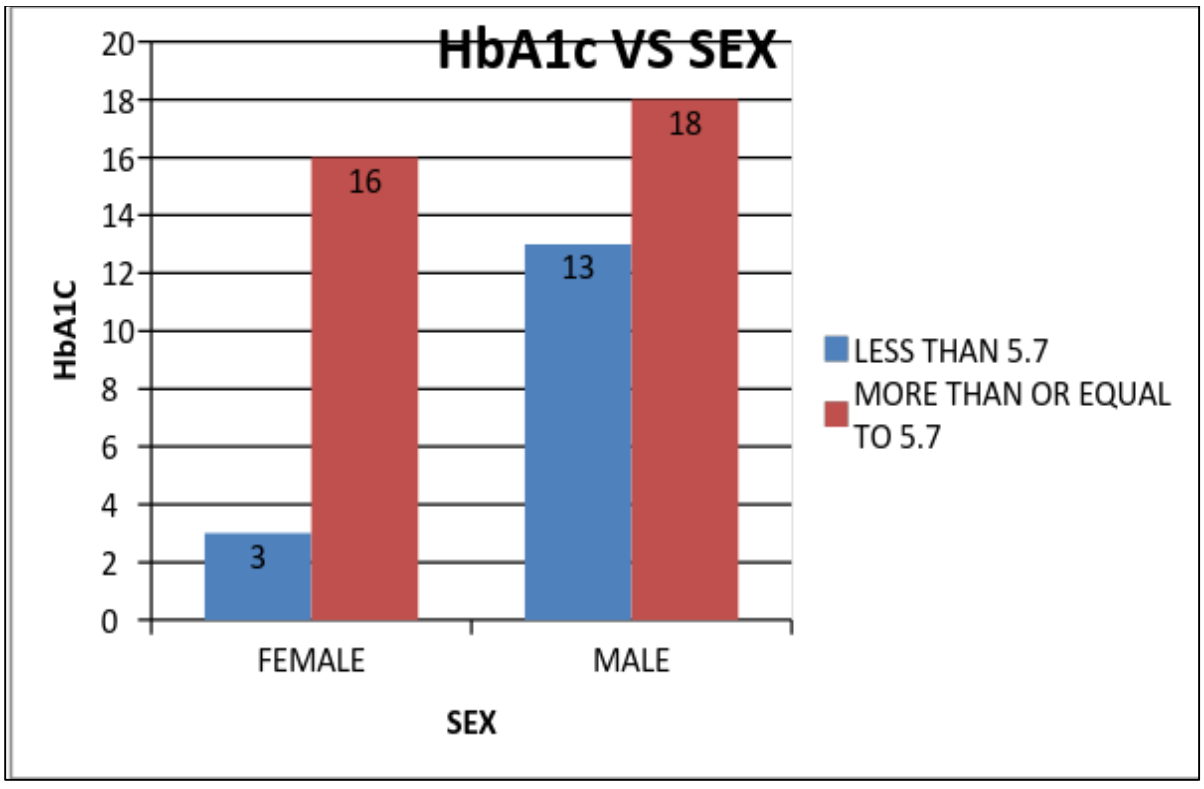
And HbA1c 6.1 had the highest frequency of Males .

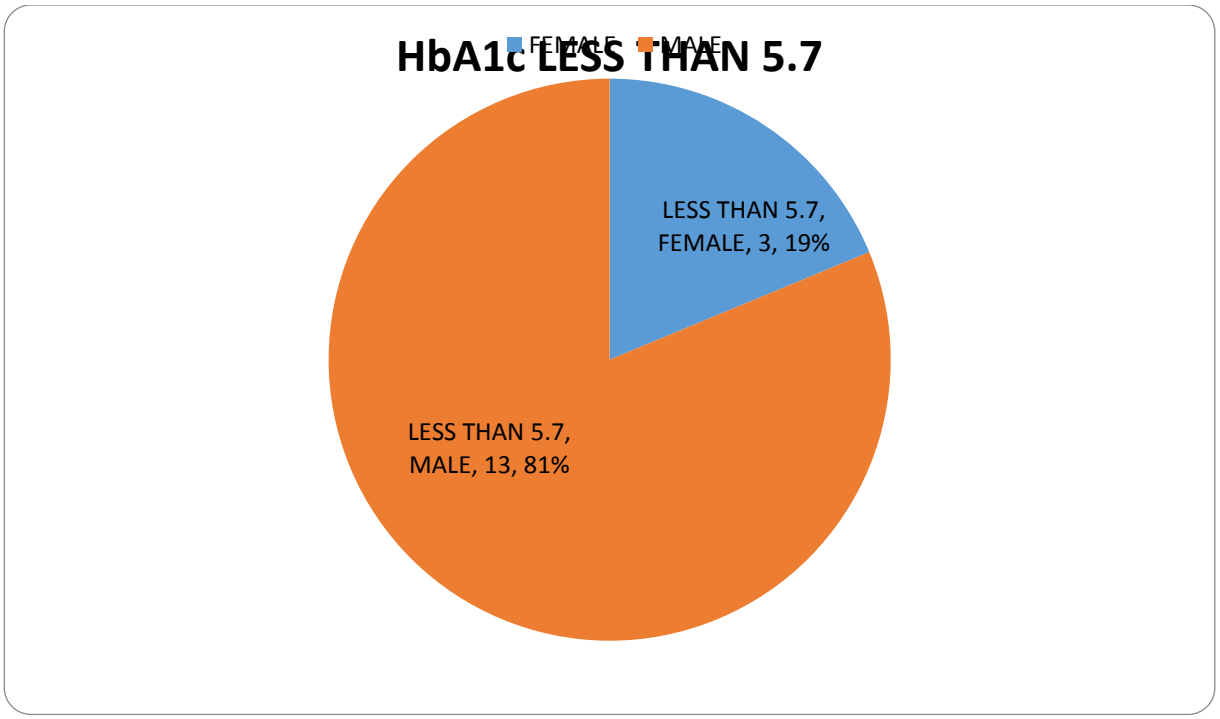
15 % of Females have HbA1c less than 5.7

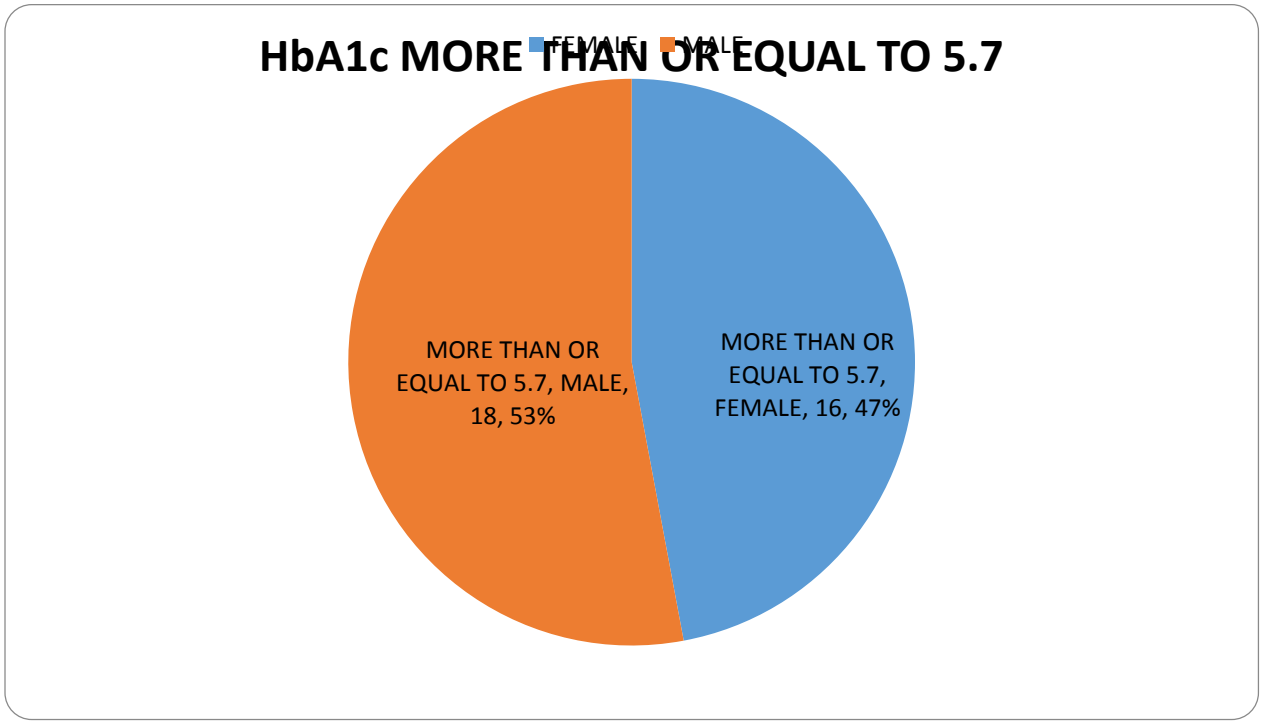
85 % of Females have HbA1c more than or equal to 5.7

42 % of Males have HbA1c less than 5.7

68 % of Males have HbA1c more than or equal to 5.7




HbA1c LESS THAN 5.7
FEMALE
MALE
LESS THAN 5.7, FEMALE, 3, 19%
LESS THAN 5.7, MALE, 13, 81%


HbA1c MORE THAN OR EQUAL TO 5.7
FEMALE
MALE
MORE THAN OR EQUAL TO 5.7, MALE, 18, 53%
MORE THAN OR EQUAL TO 5.7, FEMALE, 16, 47%

In HbA1c less than 5.7 group 81 % were Males and 19% were Females.

The frequency of Males is 4 folds when compared to Females

In HbA1c more than or equal to 5.7 group 53 % were Males and 47% were Females.

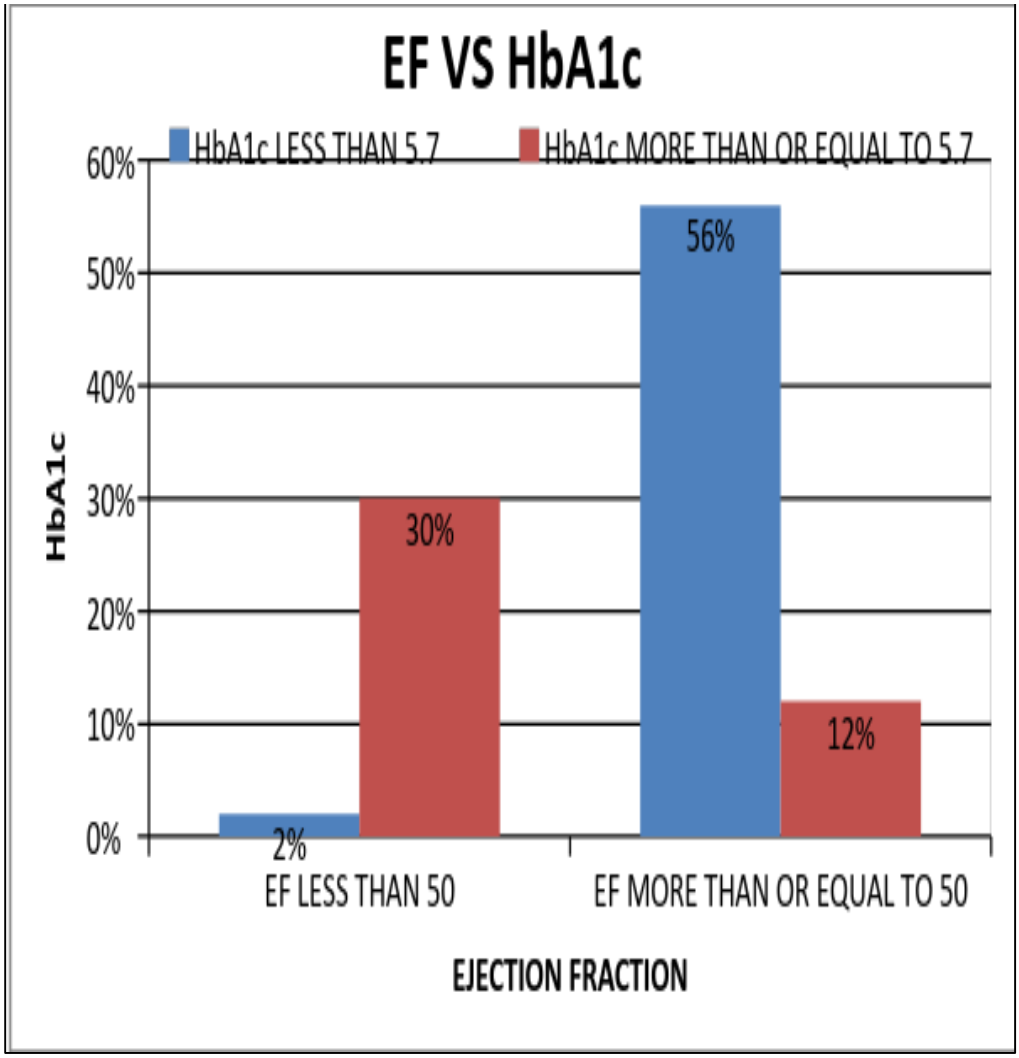
**EJECTION FRACTION AND HbA1c**

| | **HbA1C** | |
|---|---|---|
| **EF** | **LESS THAN 5.7** | **MORE THAN OR EQUAL TO 5.7** |
| **BELOW 50** | 1 | 28 |
| **MORE THAN OR EQUAL TO 50** | 15 | 6 |
| **TOTAL** | 16 | 34 |

Among the total population

29 patients ie 58 percent of total population had EF less than 50

21 patients ie 42 percent of total population had EF more than or equal 50

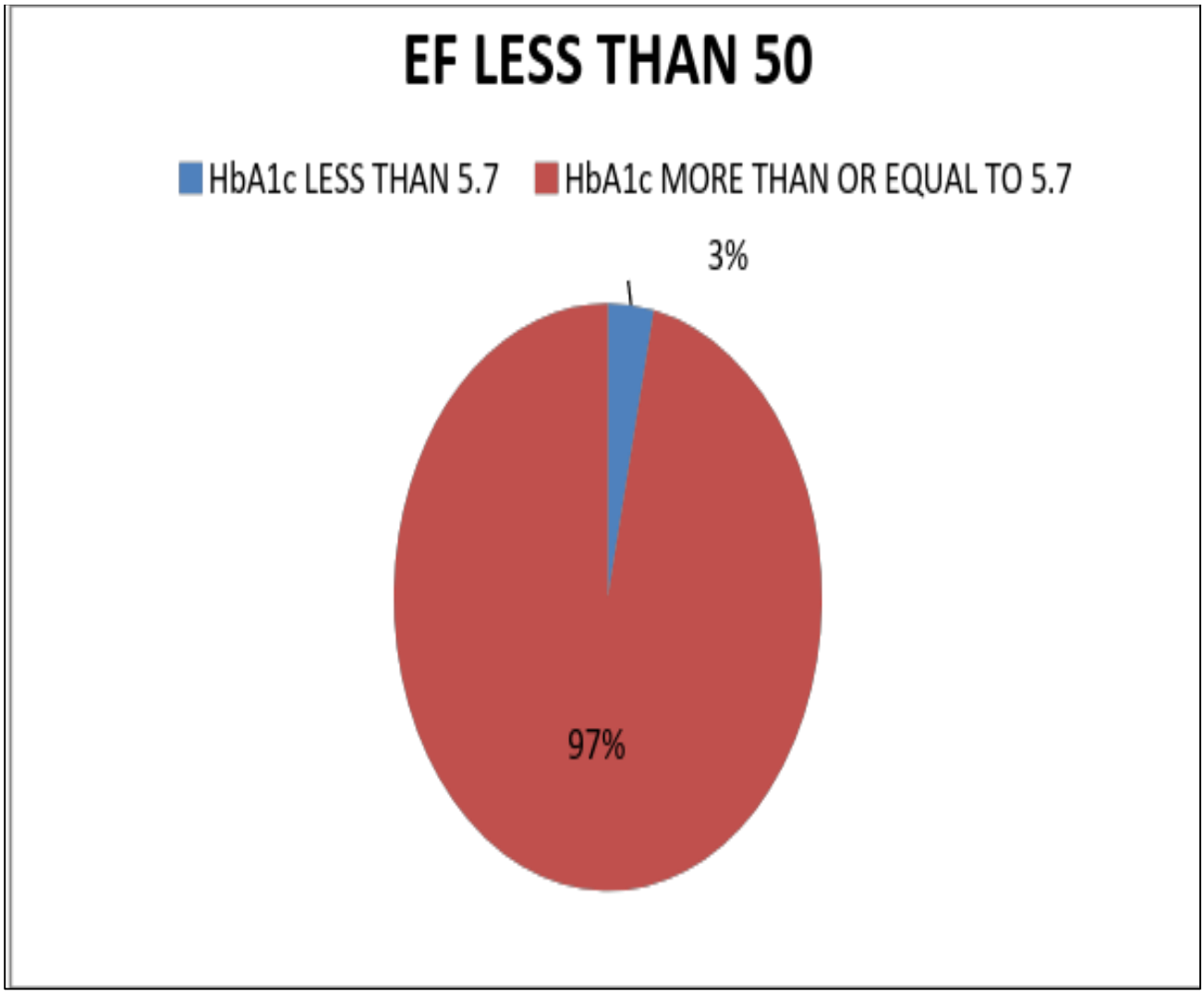


In EF less than 50 group  2% of population had HbA1c less than 5.7

and 30 % had HbA1c more than or equal to 5.7

In EF more than or equal to  50 group  56% of population had HbA1c less than 5.7

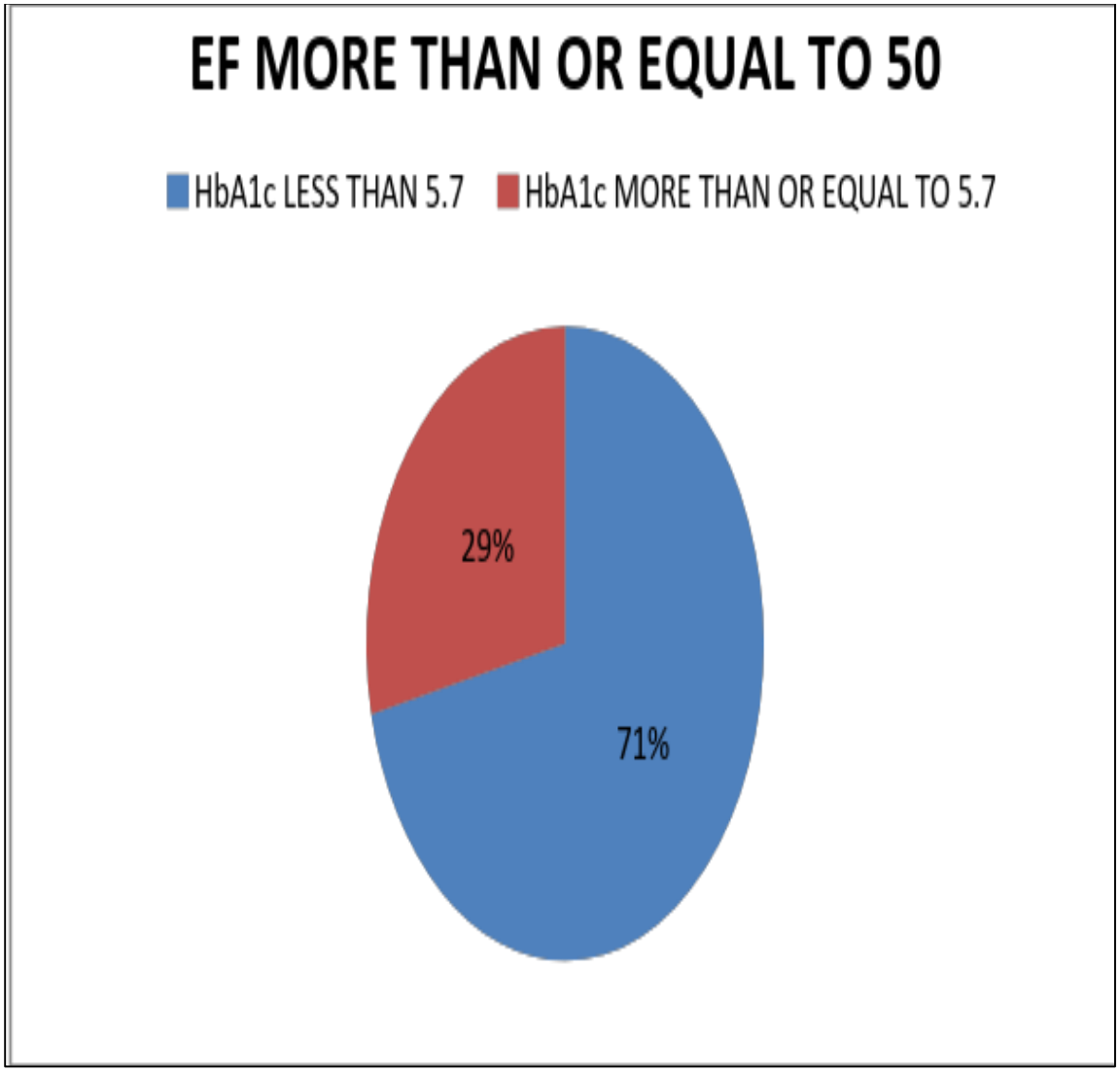
and 12 % had HbA1c more than or equal to 5.7




In EF less than 50 group 97 % of population had HbA1c more than or equal to 5.7

and 3% had HbA1c less than 5.7

The proportion of patients with HbA1c more  than or equal to 5.7 was  30 folds higher than the patients with HbA1c less than 5.7




In EF more than or equal  50 group 29 % of population had HbA1c more than or equal to 5.7 and 71 % had HbA1c less than 5.7

The proportion of patients with HbA1c less than 5.7 was 2 folds higher than the patients with HbA1c more than or equal to 5.7.

**Single Table Analysis**

| | Point | 95% Confidence Interval | |
|---|---|---|---|
| | Estimate | Lower | Upper |
| PARAMETERS: Odds-based | | | |
| **Odds Ratio (cross product)** | **0.0143** | 0.0016 | 0.1300 (T) |
| **Odds Ratio (MLE)** | **0.0162** | 0.0007 | 0.1139 (M) |
| | | 0.0003 | 0.1382 (F) |
| PARAMETERS: Risk-based | | | |
| Risk Ratio (RR) | 0.0483 | 0.0069 | 0.3376 (T) |
| Risk Difference (RD%) | -67.9803 | -88.4116 | -47.5490 (T) |
| | | | |

In this study group, more than 95 % of patients with EF <50 have HbA1c more than 5.7 . More than 70% of patients with EF ≥50 have HbA1c less than 5.7 .

When extrapolated ( for 1000 patients ) if EF <50 on1y 14 patients will have HbA1c values < 5.7.

| STATISTICAL TESTS | Chi-square | 1-tailed p | 2-tailed p |
|---|---|---|---|
| Chi-square - uncorrected | 25.8675 | | 0.0000003657 |
| Chi-square - Mantel-Haenszel | 25.3502 | | 0.0000004781 |
| Chi-square - corrected (Yates) | 22.8377 | | 0.0000017627 |
| Mid-p exact | | 0.0000001639 | |
| Fisher exact | | 0.0000003237 | 0.0000003237 |

In this study Non diabetic unstable angina patients who had EF <50 have 25 times more chance of having HbA1c more than or equal to 5.7.

In other words In this study Non diabetic unstable angina patients who had EF >50 have 25 times more chance of having HbA1c less than 5.7.

## Discussion

Our study included the first 50 Non diabetic unstable angina patients admitted in emergency ward. In the total population of 50 , Males were 31 contributing 62 % and Females were 19 contributing 38 %. The mean age of the population was 55 years and the mean age among Males and Females were 54 and 57 respectively. Among the various age groups highest population frequency was seen in age intervals 55-60 and 65 – 70. The maximum frequency of Males are in age group 56-60 .The least frequency of Males are in age group 41-45 & 61-65. The maximum frequency of Females are in age group 65-70 . The least frequency of Females are in age group less than 40 . When assessing the age group less than 40 years males had five fold increased frequency when compare to females .When assessing the age group 65- 70 years females and male have similar frequency. Significant difference in sex ratio is also seen in age group 56- 60 years . When ejection fractions of the entire population was assessed , the mean EF was found to be 52 where as the mean EF of among Males was 52 and females was 49.5 . Age group 65-70 had the highest frequency of patients with EF less than 50 . Age group less than 40 & 41- 45 had the highest frequency of patients with EF more than or equal to 50 . Highest frequency of patients were registered in EF value of 45 % which contributes to 24 % of the total population. In this study 58 percent ( 29 )

of the population had EF less than 50 %. 42 percent ( 21 ) of the population had EF more than or equal to 50 %. Thus patients with ejection fraction more than or equal to 50 are lower in frequency when compared to patients with ejection fraction less than 50. The assessment of age group less than 40 years indicate that patients with EF≥50 years have two fold increased frequency when compare to patients with EF <50 . The assessment of age group 65-70 years reveals that patients with EF<50 years have four fold increased frequency when compare to patients with EF ≥50 .The mean HbA1c of the population is 5.9 (5.91) . The mean HbA1c among Males is 5.9 ( 5.8387) and Females is 6.0 ( 6.026). 15 % of Females have HbA1c less than 5.7 .85 % of Females have HbA1c more than or equal to 5.7 . 42 % of Males have HbA1c less than 5.7 . 68 % of Males have HbA1c more than or equal to 5.7 . 32 percent of population have HbA1c less than 5.7 with a frequency of 16 subjects . 68 percent of population have HbA1c equal to or more than 5.7 with a frequency of 34 subjects. In patients with HbA1c less than 5.7 the maximum frequency of population was in age group 56-60 . In patients with HbA1c less than 5.7 the least frequency of population was in age group 61-65 & 65 – 70. In patients with HbA1c more than or equal to 5.7 the maximum frequency of population was in age groups 56-60 & 61-70 . In patients with HbA1c more than or equal to 5.7 the least frequency of population was in age groups 41-45. In the study population patients with HbA1c more than or equal to

5.7 have two fold high frequency when compared to patients with HbA1c less than 5.7 . In the study population HbA1c value of 6.1 had the maximum frequency of 9 subjects . this contributes to 18 % of the total population. In the study population patients with HbA1c more than or equal to 5.7 have two fold increased frequency when compared to patients with HbA1c less than 5.7 . In HbA1c less than 5.7 group 81 % were Males and 19% were Females. The frequency of Males is 4 folds when compared to Females in this group. In HbA1c more than or equal to 5.7 group 53 % were Males and 47% were Females. In the analysis of EF less than 50 group 2% of population had HbA1c less than 5.7 and 30 % had HbA1c more than or equal to 5.7. In EF more than or equal to 50 group 56% of population had HbA1c less than 5.7 and 12 % had HbA1c more than or equal to 5.7. In EF less than 50 group 97 % of population had HbA1c more than or equal to 5.7 and 3% had HbA1c less than 5.7 . The proportion of patients with HbA1c more than or equal to 5.7 was 30 folds higher than the patients with HbA1c less than 5.7

In EF more than or equal 50 group 29 % of population had HbA1c more than or equal to 5.7 and 71 % had HbA1c less than 5.7. The proportion of patients with HbA1c less than 5.7 was 2 folds higher than the patients with HbA1c more than or equal to 5.7. Finally In this study group, more than 95 % of patients with EF <50 have HbA1c more than 5.7 . More than 70% of patients with EF ≥50 have

HbA1c less than 5.7 . When extrapolated ( for 1000 patients ) if EF <50 on1y 14 patients will have HbA1c values < 5.7.

Thus we are able to say that Non diabetic unstable angina patients who had EF <50 have 25 times more chance of having HbA1c more than or equal to 5.7.

In other words Non diabetic unstable angina patients who had EF >50 have 25 times more chance of having HbA1c less than 5.7.

## CONCLUSION

Namitha moharthy et al [42] studied the Prognostic implications of glycated hemoglobin in nondiabetic patients with acute coronary syndrome in 47 inpatients and the results showed that complications were higher in cases with HbA1c>5.7%. This results is exactly same as our study.

Mahmod salim et al [43 ]studied the association of glycosylated haemoglobin level with the severity of coronary artery disease in NSTEMI non diabetic patients. 104 patients were included in the study and the conclusions that showed elevation of HbA1C >7% is associated with severe coronary artery disease. This was similar to our results

Manal et al [44] studied the value of admission glucose and glycosylated hemoglobin among patients with acute coronary syndrome. 57 patients were included in the study and the conclusion showed HbA1c is a powerful predictor of LV dysfunction in non diabetic NSTEMI patients. This was similar to our study

Saeed alipura [45] et al studied the value of admission hba1c levels in nondiabetic patients with unstable angina . 231patients were included in the study and their data analysis revealed that HbA1c was significantly higher in patients with EF < 50% in comparison with EF >50 % group .This was similar to our study

## LIMITATIONS OF THE STUDY

1. Sample size included in this study was relatively small. A larger number would have strengthened our understanding of the correlation between ejection fraction and HbA1c in non diabetic unstable angina patients.
2. First 50 unstable angina patients were selected without randomisation into age and sex.
3. No control groups were assigned in this study .
4. Single centred study

# THERAPEUTIC IMPLICATIONS

In our study most of Non Diabetic unstable angina patients who had ejection fraction less than 50 fall into HbA1c more than 5.7 group. If clear- cut correlation has been made among ejection fraction and HbA1c in unstable angina then question arises whether treating the patients with HbA1c between 5.7 to 6.4 improve the cardiovascular outcomes or prevent the patient from going into overt diabetes.

So I would like to suggest that a high volume multi centred study is reasonable to assess the correlation between ejection fraction and HbA1c in Non diabetic unstable angina patients .

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# ABBREVIATIONS

ACS- Acute Coronary Syndrome

DM- Diabetes Mellitus

HbA1C – Haemoglobin A1C

LDL – Low Density Lipoprotein

HDL – High Density Lipoprotein

CAD- Coronary Artery Disease

STEMI – ST elevation myocardial infarction

NSTEMI- Non ST elevation myocardial infarction

EF- Ejection Fraction

**QUESTIONNAIRE PROFORMA**

**A STUDY ON CORRELATION OF EJECTION FRACTION AND HBA1C AMONG NON DIABETIC UNSTABLE ANGINA PATIENTS**

**NAME:**
**AGE:**
**SEX:**
**ADDRESS:**
**TELEPHONE NUMBER:**
**OCCUPATION:**
**HISTORY OF DIABETES MELLITUS**
**DRUG HISTORY:**
**PERSONAL HISTORY:**
**Alcoholism**
**Smoker**
**HISTORY: h/o of chest pain**
**h/o of previous IHD**
**h/o systemic hypertension**
**h/o CKD**
**h/o surgeries**
**h/o alcohol consumption /drinking pattern**
**h/o smoking (in pack years)**
**h/o Anemia, blood loss, recent blood transfusion**

**EXAMINATION**
**HEIGHT:**
**WEIGHT:**
**BMI:**
**PULSE RATE:**
**PERIPHERAL PULSES EXAMINATION:**
**BLOOD PRESSURE**

**PALLOR / ICTERUS/ CYANOSIS/ CLUBBING / PEDAL EDEMA**

**SYSTEM WISE EXAMINATION:**
**CVS:**
**RS:**
**P/A:**
**CNS:**

**INVESTIGATIONS**
**Complete blood count:**
**Hb:**
**ESR:**
**TC:**
**DC:**

**HbA1c**

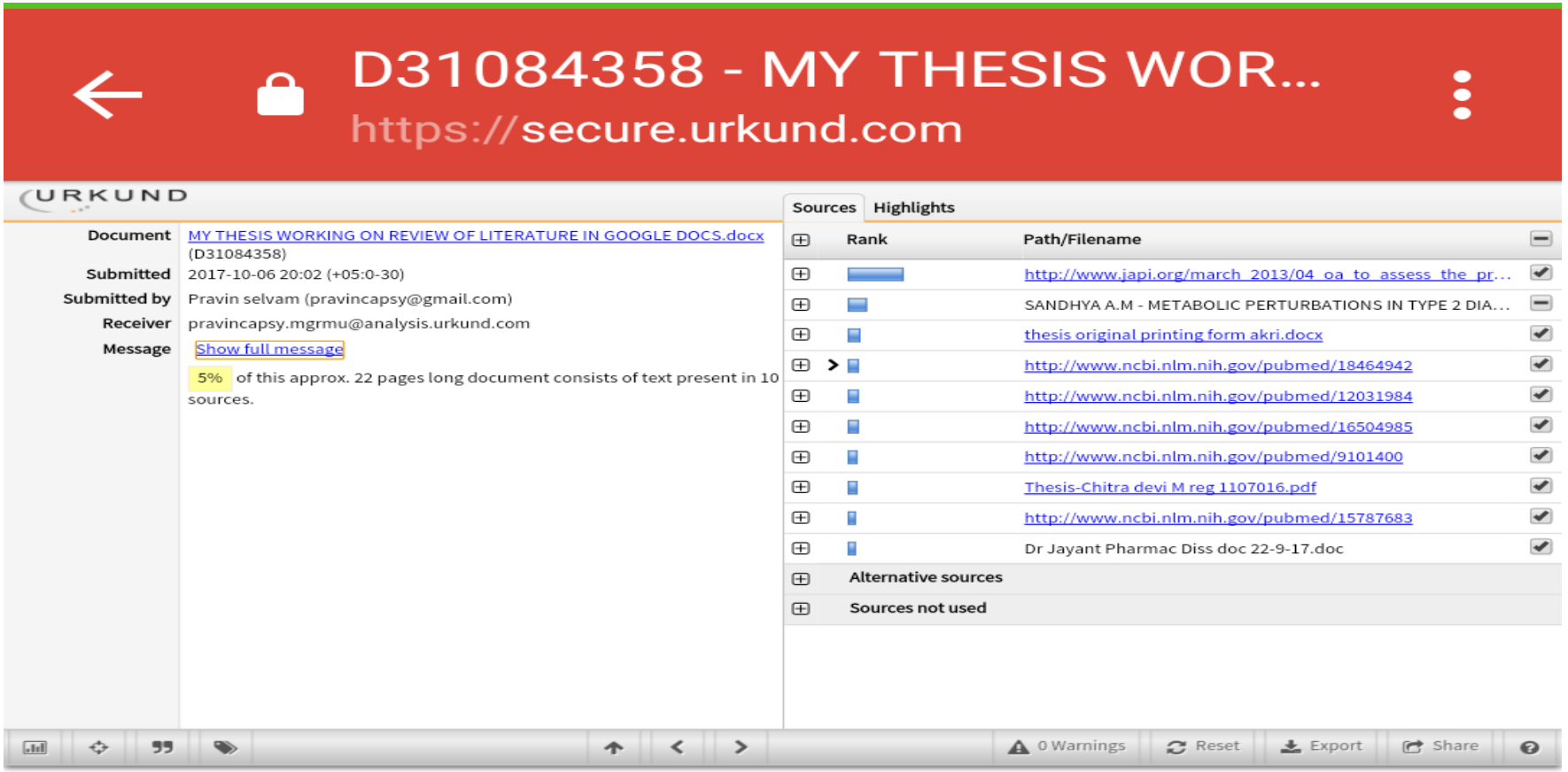
**SERIAL ECG**

**ECHOCARDIOGRAPHY**

**TROPONIN I**
**CPK - MB**

| 1 | NAME | AGE | SEX | HbA1c | EF | ef above 50 | EF BELOW 50 |
|---|---|---|---|---|---|---|---|
| 2 | ELLAPAN | 39 | M | 4.9 | 68 | 1 | 0 |
| 3 | RAJENDRAN | 68 | M | 5.5 | 65 | 1 | 0 |
| 4 | IMRAN | 56 | M | 6.3 | 52 | 1 | 1 |
| 5 | NATARAJAN | 40 | M | 5.4 | 68 | 1 | 0 |
| 6 | SARAVANAN | 58 | M | 6.4 | 48 | 0 | 1 |
| 7 | SHANTHI | 64 | F | 6.4 | 45 | 0 | 1 |
| 8 | SIVAGAMI | 47 | F | 6.1 | 45 | 0 | 1 |
| 9 | MEERUN NISHA | 55 | F | 5.9 | 55 | 0 | 1 |
| 10 | ARUMUGAM | 56 | M | 6.3 | 48 | 0 | 1 |
| 11 | MANICKAM | 60 | M | 6.4 | 48 | 0 | 1 |
| 12 | ESWARI | 42 | F | 5.2 | 68 | 1 | 0 |
| 13 | GOPINATH | 55 | M | 5.3 | 62 | 1 | 0 |
| 14 | USMAN | 70 | M | 5.9 | 45 | 0 | 1 |
| 15 | ELAIYAMMAL | 62 | F | 6.3 | 40 | 0 | 1 |
| 16 | PAAPA | 51 | F | 6.1 | 48 | 0 | 1 |
| 17 | MOHAN | 44 | M | 5.3 | 68 | 1 | 0 |
| 18 | KARTHIKEYAN | 54 | M | 6.2 | 40 | 0 | 1 |
| 19 | NADHAMUNI | 62 | M | 6.1 | 45 | 0 | 1 |
| 20 | VAIRAVAN | 70 | M | 5.9 | 45 | 0 | 1 |
| 21 | SAANTHAKUMARI | 63 | F | 5.3 | 55 | 1 | 0 |
| 22 | AROKIAM | 66 | F | 6.2 | 48 | 0 | 1 |
| 23 | CHINNAKULANDHAI | 66 | F | 5.9 | 40 | 1 | 1 |
| 24 | SEVANTHI | 45 | F | 5.8 | 63 | 1 | 1 |
| 25 | VELU | 47 | M | 6.1 | 45 | 0 | 1 |
| 26 | KUPPUSAMY | 66 | M | 6.3 | 45 | 0 | 1 |
| 27 | PURUSHOTHAMAN | 62 | M | 6 | 60 | 1 | 1 |

| | A | B | C | D | E | F | G | H |
|---|---|---|---|---|---|---|---|---|
| 24 | SEVANTHI | 45 | F | 5.8 | 63 | 1 | 1 | |
| 25 | VELU | 47 | M | 6.1 | 45 | 0 | 1 | |
| 26 | KUPPUSAMY | 66 | M | 6.3 | 45 | 0 | 1 | |
| 27 | PURUSHOTHAMAN | 62 | M | 6 | 60 | 1 | 1 | |
| 28 | KANNATHAL | 70 | F | 6.4 | 45 | 0 | 1 | |
| 29 | KALIDAS | 42 | M | 5.5 | 60 | 1 | 0 | |
| 30 | RAMALINGAM | 56 | M | 6.1 | 48 | 0 | 1 | |
| 31 | SIVAPRAKASAM | 40 | M | 5.5 | 65 | 1 | 0 | |
| 32 | MUTHU | 49 | M | 6.1 | 52 | 1 | 1 | |
| 33 | SUDALAI | 58 | M | 5.6 | 65 | 1 | 0 | |
| 34 | KUMAR | 50 | M | 5.6 | 60 | 1 | 0 | |
| 35 | BALAJI | 40 | M | 6.2 | 42 | 0 | 1 | |
| 36 | KUPPAMAL | 70 | F | 6.2 | 45 | 0 | 1 | |
| 37 | AROKIAMARY | 51 | F | 5.7 | 48 | 0 | 1 | |
| 38 | SHENWAZ | 68 | F | 6.1 | 40 | 0 | 1 | |
| 39 | ANTONY | 63 | M | 6.3 | 45 | 0 | 1 | |
| 40 | IRULAPPAN | 67 | M | 6.1 | 40 | 0 | 1 | |
| 41 | MUNIAMMAL | 47 | F | 6.2 | 45 | 0 | 1 | |
| 42 | VIJAYAN | 47 | M | 5.5 | 64 | 1 | 0 | |
| 43 | NAZEER AHMED | 57 | M | 5.1 | 55 | 1 | 0 | |
| 44 | BALAKRISHNAN | 48 | M | 6.2 | 48 | 0 | 1 | |
| 45 | PICHAMMAL | 56 | F | 6.4 | 45 | 0 | 1 | |
| 46 | NAKEERAN | 55 | M | 5.6 | 60 | 1 | 0 | |
| 47 | SITADEVI | 40 | F | 6.3 | 48 | 0 | 1 | |
| 48 | CATHRENE JOSEPH | 58 | F | 5.6 | 66 | 1 | 0 | |
| 49 | POONGOTHAI | 65 | F | 6.4 | 40 | 0 | 1 | |
| 50 | DHANASEKAR | 40 | M | 6.1 | 52 | 1 | 1 | |
| 51 | PALANIVEL | 59 | M | 6.2 | 46 | 0 | 1 | |




A STUDY ON CORRELATION OF EJECTION FRACTION AND HBA1C AMONG NON DIABETIC UNSTABLE ANGINA PATIENTS Introduction regarding HbA1c Dr. Huisman and Meyering were the first to isolate Hemoglobin A1c from other different types of Hemoglobin(1) . They used chromatographic column method for isolation of HbA1c in 1958. HbA1c was initially portrayed as a glycoprotein by Bookchin and Gallop in 1968 however its increase in patients with diabetes Mellitus was depicted by Samuel et al in 1969. The use for HbA1c as monitoring tool in the control of blood sugar levels in diabetic patients was proposed in 1976 by Anthony Ceremy . The nomenclature came from the fact , on the basis of cation exchange chromatography the first separated hemoglobin is HbA . On the order of elution they are further subclassified into HbA1a HbA1b , HbA1c. The pathogenesis of HbA1c causing damage to the body metabolism is by two distinct process (2 ). First is by increasing the highly reactive free radicals which are present in the blood cells .These free radicals also alter the blood cell membranes . These alterations lead to increased blood cell aggregation which further leads to increased blood viscosity resulting in impaired blood flow through the organs. Second mechanism is by increasing the inflammatory process finally resulting in atherosclerotic plaque, these changes finally Impact the permeability of the inner surface of the endothelium causing leakage. The production of Pro- inflammatory proteins like Monocyte Adhesion Protein which promotes the aggregation of macrophages in the vessel wall is also elevated leading to atheroma formation. This glycated hemoglobin pass through the vascular smooth muscle causing inactivation of acetylcholine induced endothelial relaxation by its affinity and bonding to nitric oxide preventing the normal

# INSTITUTIONAL ETHICAL COMMITTEE, STANLEY MEDICAL COLLEGE, CHENNAI-1

Title of the Work : Prognostic Valve of HBA1C in non Diabetic unstable Angina patients Admitted in tertiary care Hospital.

Principal Investigator : Dr. S Pravin Selvam

Designation : PG MD (General Medicine)

Department : Department of General Medicine
Government Stanley Medical College,
Chennai-01

The request for an approval from the Institutional Ethical Committee (IEC) was considered on the IEC meeting held on 24.02.2017 at the Council Hall, Stanley Medical College, Chennai-1 at 2PM

The members of the Committee, the secretary and the Chairman are pleased to approve the proposed work mentioned above, submitted by the principal investigator.

The Principal investigator and their team are directed to adhere to the guidelines given below:

1. You should inform the IEC in case of changes in study procedure, site investigator investigation or guide or any other changes.
2. You should not deviate from the area of the work for which you applied for ethical clearance.
3. You should inform the IEC immediately, in case of any adverse events or serious adverse reaction.
4. You should abide to the rules and regulation of the institution(s).
5. You should complete the work within the specified period and if any extension of time is required, you should apply for permission again and do the work.
6. You should submit the summary of the work to the ethical committee on completion of the work.

8/6/17

MEMBER SECRETARY,
IEC, SMC, CHENNAI

MEMBER SECRETARY
ETHICAL COMMITTEE,
STANLEY MEDICAL COLLEGE
CHENNAI-600 001.